SUPPLEMENT 1

Effect of First-Line Serplulimab vs Placebo Added to Chemotherapy on Survival in Patients with Extensive-Stage Small Cell Lung Cancer: The ASTRUM-005 Randomized Clinical Trial

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This supplement contains the following items:

1. Original protocol
2. Final protocol
3. Summary of changes to the protocol
4. Statistical analysis plan

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A Randomized, Double-Blind, Multicenter, Phase III Study to Evaluate HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin-Etoposide) in Previously Untreated Patients with Extensive Stage Small Cell Lung Cancer (ES-SCLC)

Clinical Trial l Protocol

Investigational Product	HLX10
Protocol Number	HLX10-005-SCLC301
EudraCT	2019-XXXXXX-XX
Sponsor	Shanghai Henlius Biotech, Inc.7/F,Innov Tower, Zone A, No.1801 HongMei Rd, Xuhui District, Shanghai, 200233 China
Study Phase	III
Indication	Previously Untreated and Extensive Stage Small Cell Lung Cancer (ES-SCLC)
Leading Site	Jilin Cancer Hospital
Principal Investigator	Professor Cheng Ying
Version No.	V1.0
Version Date	4 Mar., 2019

Signature Page for Principal Investigator (Leading Site)

I have read and become familiar with this protocol, confirmed the schedule in the protocol and the necessary contents including the implementation, and clearly understood the responsibilities related to this trial protocol. I agree to, and will perform my duties in strict accordance with the laws and regulations of local authority, Declaration of Helsinki, Good Clinical Practice and this protocol.

Leading Site: Jilin Cancer Hospital

Professor Cheng Ying (Signature)	Date of Signing (dd/mm/yyyy)

Signature Page for Principal Investigator (Participating Site)

I have read and become familiar with this protocol, confirmed the schedule in the protocol and the necessary contents including the implementation, and clearly understood the responsibilities related to this trial protocol. I agree to, and will perform my duties in strict accordance with the laws and regulations of local authority, Declaration of Helsinki, Good Clinical Practice and this protocol.

Principal Investigator (Print)	Principal Investigator (Signature)
Study Site	Date of Signing (dd/mm/yyyy)

Signature Page for Sponsor

I have read and become familiar with this protocol, confirmed the schedule in the protocol and the necessary contents including the implementation, and clearly understood the responsibilities related to this trial protocol. I agree to, and will perform my duties in strict accordance with the laws and regulations of local authority, Declaration of Helsinki, Good Clinical Practice and this protocol.

Sponsor: Shanghai Henlius Biotech, Inc.

Eugene Liu, Vice President for Medical Affairs (Signature)	Date of Signing (dd/mm/yyyy)
Cheng Jiancheng, Director of Biostatistics (Signature)	Date of Signing (dd/mm/yyyy)

Table of Contents

TABLE OF CONTENTS **1**

ABBREVIATIONS **5**

SYNOPSIS **8**

STUDY PROCEDURES **24**

1 INTRODUCTION **28**

1.1 Disease Background and Treatment Status 28
1.2 Research Development and Basis for Dose Selection 29
1.2.1 Introduction to HLX10 29
1.2.2 Non-clinical studies on HLX10 29
1.2.3 Clinical studies of HLX10 35
1.2.4 Basis for selection of chemotherapy as a control group 36
1.2.5 Basis for combined treatment 36
1.2.6 Basis for HLX10 dose selection 37
1.3 Assessment for Risks and Benefits 37
1.3.1 Potential benefits 37
1.3.2 Identified and potential risks 38
1.3.3 Overall benefits: risk and ethical assessment 39

2 OBJECTIVES **39**

2.1 Primary Objective 39
2.2 Secondary Objective 39

3 STUDY PROTOCOL **40**

3.1 Overall Study Design 40
3.2 Endpoints 40
3.2.1 Primary endpoint 40
3.2.2 Secondary endpoints 40
3.3 Randomization, Blinding, and Unblinding 41
3.4 Number of Subjects 41
3.5 Eligibility 42
3.5.1 Inclusion criteria 42
3.5.2 Exclusion criteria 44
3.5.3 Criteria for discontinuation 47
3.6 Early Termination of Study/Closure of Study Site 48
3.7 Study Treatment 48
3.7.1 Information on study drugs 48
3.7.2 Route of administration and dosage 49
3.7.3 Dose modification 50
3.7.4 Packaging and labeling 55
3.7.5 Storage, management, and dispensing 56

3.7.6 Concomitant medication 56
3.7.7 Medication compliance 58

4 STUDY PROCEDURES AND VISITS 58

4.1 STUDY PROCEDURES 58
4.1.1 Demographics and medical history 58
4.1.2 Prior and concomitant medications 58
4.1.3 Adverse events 59
4.1.4 Quality of life assessment 59
4.1.5 Echocardiography 60
4.1.6 12-lead ECG 61
4.1.7 Complete physical examination 61
4.1.8 Symptom-directed physical examination 61
4.1.9 Height, weight and vital signs 61
4.1.10 ECOG scores 61
4.1.11 Local laboratory tests 62
4.1.12 Central laboratory assessments 63
4.1.13 Tumor imaging 64
4.1.14 Biomarker sample collection 65
4.2 SCREENING PERIOD (DAY -28 TO -1) 66
4.3 TREATMENT PERIOD 67
4.4 END-OF-TREATMENT VISIT 71
4.5 FOLLOW-UP PERIOD 72
4.5.1 Safety follow-up period 72
4.5.2 Survival follow-up 73
4.6 STUDY ASSESSMENTS 74
4.6.1 Efficacy assessment 74
4.6.2 Safety assessment 74
4.7 ADVERSE EVENTS 74
4.7.1 Definition of AE 74
4.7.2 Definition of SAE 77
4.7.3 Documentation of AEs 79

5 OTHER REASONABLE INTERPRETATIONS 81

5.1 Determination of Predictability 82
5.2 Reporting of SAEs 83
5.3 Follow-Up of AEs 84
5.4 Pregnancy 84

6 STATISTICAL METHODOLOGY 85

6.1 SAMPLE SIZE ESTIMATION 85
6.2 BLINDED SAMPLE SIZE RE-ESTIMATION 85
6.3 STATISTICAL ANALYSIS SETS 86
6.3.1 Intent-to-treat (ITT) set 86
6.3.2 Per protocol set (PPS) 86

6.3.3 Safety set (SS) 86
6.3.4 Pharmacokinetic set (PKS) 86
6.4 INTERIM ANALYSIS AND FINAL ANALYSIS 86
6.5 STATISTICAL ANALYSIS METHODS 87
6.5.1 Demographics, medical history, and baseline characteristics 87
6.5.2 Medication compliance 87
6.5.3 Efficacy analysis 87
6.5.4 Safety analysis 89
6.5.5 Pharmacokinetic analysis and immunogenicity analysis 89
6.5.6 Biomarker analysis 89
6.5.7 Analysis of subject-reported outcome variables 89

7 ETHICS 90

7.1 ETHICAL REQUIREMENTS 90
7.2 INFORMED CONSENT 90
7.3 CONFIDENTIALITY FOR THE SUBJECT 91

8 DATA MANAGEMENT 91

8.1 DATABASE SETUP 91
8.2 DATA CHECKS 91
8.3 DATABASE LOCK 92

9 STUDY MANAGEMENT 92

9.1 QUALITY CONTROL AND QUALITY ASSURANCE 92
9.1.1 Training 93
9.1.2 Clinical monitoring 93
9.1.3 Audit 94
9.1.4 Data management 94
9.1.5 Missing and useless data 95
9.2 DOCUMENTATION AND RETENTION OF STUDY DATA 95
9.3 FOLLOW-UPS AND MEDICAL MEASURES AFTER STUDY COMPLETION 95

10 RESPONSIBILITIES 96

10.1 RESPONSIBILITIES OF THE INVESTIGATOR 96
10.2 RESPONSIBILITIES OF THE SPONSOR 97

11 CONFIDENTIALITY AND PUBLICATION OF TRIAL RESULTS 98

12 REFERENCE 98

13 APPENDICES 101

APPENDIX 1: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS 101
APPENDIX 2-1: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST 1.1) 102
APPENDIX 2-2: MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS 108
APPENDIX 3:QUALITY OF LIFE SCALE EORTC QLQ-C30, EQ-5D-5L, EORTC QLQ-LC13 113
ANNEX 4: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) - PERFORMANCE STATUS SCALE 119

APPENDIX 5: FRIDERICIA CORRECTION FORMULA 120
APPENDIX 6: COCKCROFT AND GAULT FORMULA 121
APPENDIX 7: HEART FUNCTIONAL CLASSIFICATION OF NEW YORK HEART ASSOCIATION 122
APPENDIX 8: GUIDELINES FOR DOSE MODIFICATION AND TREATMENT FOR IMMUNE-RELATED TOXICITY 123
APPENDIX 9: PROHIBITED TRADITIONAL CHINESE MEDICINES 146

List of Tables

TABLE 1. PRINCIPLES FOR CHEMOTHERAPY MODIFICATIONS 53
TABLE 2. CARBOPLATIN MODIFICATIONS FOR HEMATOLOGICAL TOXICITIES 53
TABLE 3. CARBOPLATIN DOSING MODIFICATIONS BASED ON NON-HEMATOLOGICAL TOXICITIES IN PREVIOUS TREATMENTS 54
TABLE 4. ETOPOSIDE DOSING MODIFICATION FOR SUBJECTS WITH RENAL IMPAIRMENT 55
TABLE 5. LOCAL LABORATORY TESTS 62
TABLE 6. PK AND ADA BLOOD SAMPLING 64
TABLE 7. EVALUATION OF CAUSALITY BETWEEN AE AND STUDY DRUG 82

List of Figures

FIGURE 1. OVERALL STUDY DESIGN 23
FIGURE 2. SCHEMATIC OF STUDY TREATMENT 69

Abbreviations

Abbreviation	Explanation
ADA	Anti-drug antibody
AE	Adverse events
ALT	Alanine transaminase
ANC	Absolute neutrophil count
APTT	Activated partial prothrombin time
ASCO	American Society of Clinical Oncology
AST	Aspartic transaminase
ATC	Anatomical, Therapeutic and Chemical Classification System
BUN	Blood urea nitrogen
CHO	Chinese hamster ovary cells
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel test
CR	Complete response
Cr	Creatinine
CRA	Clinical research associate
CRO	Contract research organization
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DCR	Disease control rate
DFS	Disease free survival
DOR	Duration of response
12-ECG	12 lead electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture system
ES-SCLC	Extensive stage small cell lung cancer
EQ-5D-5L	5-level EQ-5D version
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Scale
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FFPE	Formalin-fixed paraffin embedded
FT3	Free triiodothyronine

Abbreviation	Explanation
FT4	Free thyroxine
GCP	Good Clinical Practice
Hb	Haemoglobin
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HR	Hazard Ratio
HRQoL	Health-related quality of life
HIV	Human immunodeficiency virus
ICF	Informed consent form
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
IRC	Independent Review Committee
IRRC	Independent Radiology Review Committee
ITT	Intent-to-treatment set
IVIG	Intravenous immunoglobulin
IWRS	Interactive web response system
LFT	Liver function test
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NMPA	National Medical Products Administration
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PCP	Pneumocystis pneumonia
PD	Progressive disease
PD-L1	Programmed cell death-ligand 1
PET-CT	Positron emission tomography - computerized tomography
PD-1	Programmed cell death-ligand 1
PFS	Progression-free survival
PI	Principal Investigator

Abbreviation	Explanation
PK	Pharmacokinetics
PKS	PK set
PLT	Platelet
PPS	Per protocol set
PR	Partial response
QC	Quality control
RECIST	Response Evaluation Criteria in Solid Tumors
RO	Receptor occupancy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety analysis set
SCLC	Small cell lung cancer
SD	Stable disease
SOP	Standard operating procedure
SS	Safety set
T3	Triiodothyronine
T4	Thyroxine
TB	Total bilirubin
TEAE	Treatment emergent adverse event
TMB	Tumor mutation burden
TNF-α	Tumor necrosis factor α
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	Ultrasound
VALG	Veterans Administration Lung Study Group
irAEs	Immune-related adverse events

Synopsis

Investigational Product	HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection)
Active Ingredient	Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection
Title	A Randomized, Double-Blind, Multicenter, Phase III Study to Evaluate HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin-Etoposide) in Previously Untreated Patients with Extensive Stage Small Cell Lung Cancer (ES-SCLC)
Protocol Number	HLX10-005-SCLC301
Sponsor	Shanghai Henlius Biotech, Inc.
Trial Phase	Registered Clinical Phase III Study
Study Sites	60-70 sites worldwide
Subjects	Patients with extensive stage small cell lung cancer (ES-SCLC)
Objectives	**Primary Objective** • To evaluate the clinical efficacy of HLX10 combining with chemotherapy versus placebo combining with chemotherapy in previously untreated patients with ES-SCLC. **Secondary Objectives** • To evaluate the safey and tolerabilityof HLX10 combining with chemotherapy versus placebo combining with chemotherapy in previously untreated patients with ES-SCLC. • To measure the exposure following HLX10 administration Exploratory • Exploratory population pharmacokinetic (PopPK) analysis
Stages	This trial is divided into three stages: screening (28 days), treatment (until loss of clinical benefit, death, intolerable toxicity, withdrawal of informed consent, or occurrence of other reasons specified in the protocol, whichever

	occurs first), and follow-up (including safety follow-up period and survival follow-up period).
Planned Enrollment	Approximately 489 (326 for HLX10 and 163 for placebo)
Study Design	This is a randomized, double-blind, multicenter, clinical Phase III study to evaluate the clinical efficacy, safety and tolerability of HLX10 or placebo in combination with chemotherapy in patients with previously untreated ES-SCLC, to collect PK parameters and to investigate the biomarker related to efficacy. Subjects in this study will be randomized to arm A or B at 2:1 ratio as follows: • Arm A (HLX10): HLX10 + chemotherapy (carboplatin-etoposide) • Arm B (control): placebo + chemotherapy (carboplatin-etoposide) Randomization are stratified by PD-L1 expression level (negative, positive, not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years). After screening, subjects meeting the inclusion criteria and not meeting the exclusion criteria will be enrolled. Included subjects will be treated with HLX10 or placebo in combination with chemotherapy once every 3 weeks, until loss of clinical benefit, death, intolerable toxicity, withdrawal of informed consent, or occurrence of other reasons specified in the protocol (whichever occurs first). Treatment should be discontinued when they have evidence of disease progression as assessed by RECIST v1.1. However, considering the limited availability and efficacy or greater toxicity of treatment options after withdrawal, and for better adaptation to standard clinical practice, the subject who **meets all the following conditions** may continue the treatment as determined by the investigator and after appropriate discussion with the subject and obtaining the informed consent. (1) With no clinical signs and symptoms (including worsening of laboratory findings) indicating a significant disease progression. (2) A stable Eastern Cooperative Oncology Group (ECOG) performance status score.

	(3) No rapid disease progression or tumor progression requiring urgent alternative medical intervention at critical anatomical sites (e.g., spinal cord compression). (4) The major organ function meets the inclusion and exclusion criteria of this study. (5) The subject should sign the supplementary informed consent formto continue treatment. The primary objective of this study is to compare the PFSs of HLX10 in combination with chemotherapy versus placebo in combination with chemotherapy, as assessed by an Independent Radiology Review Committee (IRRC) using RECIST v1.1.
Study Drugs, Dosage, Regimen and Route of Administration	This study drugs are administered as per a every 3-week (21-day) cycle as follows: **<u>Investigational product: HLX10 or placebo</u>** 4.5 mg/kg by intravenous infusion (IV) on Day 1 of each 3-week (21-day) cycle. **<u>Other study drugs: combined chemotherapy</u>** The following regimen will be given every 21-day (3-week) cycle for a maximum of 4 cycles. • Etoposide: 100 mg/m^2, IV, on Days 1, 2, and 3 of each cycle. • Carboplatin: AUC = 5, IV, on Day 1 of each cycle up to a dose of 800 mg. Refer to Figure 2 "Schematic of study treatment" for the regimen of each treatment arm. On Day 1 of dosing in each treatment cycle, subjects are given HLX10 or placebo intravenously first, followed by intravenous carboplatin + etoposide. Vital signs are closely monitored during the administration. HLX10 or placebo is administered via a blinded infusion, carboplatin + etoposide (up to 4 cycles) via an open-label infusion, and subjects will continue receiving

	etoposide on Days 2 and 3. Treatment with study drug will continue until disease progression, intolerable toxicity, discontinuation decided by subject or investigator, death, withdrawal of informed consent, pregnancy, incompliance with protocol or procedure requirements, administrative reasons, or other reasons specified in the protocol, whichever occurs first. If chemotherapy is not used due to toxicity or other reasons in a certain cycle, it is not counted as the number of combined chemotherapy cycles. After completing 4 cycles of chemotherapy, even if the subject does not meet the above criteria, the chemotherapy will not be continued.
Prophylactic Medications, Dosage and Method	Prophylactic and other supportive treatment for nausea and vomiting may be given according to local medical practice before and after carboplatin and etoposide administration.
Dose Modification	**General Principles for Dose Modification** Any modified or delayed doses should be recorded in the source document and eCRFs. Adverse events are assessed for severity according to CTCAE v4.03. • For concomitant conditions already present at baseline, dose modifications may be determined by the investigator based on changes in severity of toxicity. For example, if the subject already has a Grade 1 weakness at baseline, and the severity increases to Grade 2 during treatment, it may be considered to make dose modification according to Grade 1 toxicity due to 1-grade increase in toxicity. • If multiple toxicities of different severities occur at the same time, the dose should be adjusted according to the most severe toxicity. • If the toxicity is related to one of the study drugs only (for example, HLX10, carboplatin or etoposide) as assessed by the investigator, dose modification of that study drug only with reference to the corresponding dose modification principle is acceptable, and the subject can continue receiving the other study treatment in the absence of other contraindications.

- If the toxicity is associated with only one of the chemotherapy medications as assessed by the investigator, the dose of the other chemotherapy medication may not be adjusted.
- In the event that a delay is required for reasons of toxicity (not definitively related to which drug), similar delays of all study drugs at the same time are required if recovery to a re-dosing level is expected within 2 weeks.
- If HLX10/placebo, carboplatin, or etoposide is interrupted due to toxicity, study treatment must be restarted, keeping HLX10/placebo in sync with the chemotherapy treatment cycles.

Principles for Chemotherapy Modification

In the event of intolerance to etoposide/carboplatin, the dose may be modified with reference to the following principles.

Dose Level	Etoposide Dosing Regimen	Carboplatin Dosing Regimen
Starting Dose	100 mg/m^2, IV, on Days 1, 2, and 3 of each 3-week (21-day) cycle	AUC = 5, NMT 800 mg, IV, on Day 1 of each 3-week (21-day) cycle
First Dose Reduction	75% of starting dose	75% of starting dose
Second Dose Reduction	50% of starting dose	50% of starting dose

If treatment is delayed due to intolerance to chemotherapy, chemotherapy may be delayed to the next cycle of administration, with the maximum permissible interval for chemotherapy not exceeding 6 weeks.**Principles for HLX10 or Placebo Modification**

In the event of HLX10- or placebo-related toxicity, a delay in HLX10 or placebo is allowed rather than dose adjustment. Subjects who miss a scheduled infusion should be actively contacted to arrange another visit as soon as possible for administration. Administration of HLX10 or placebo may be delayed, but a dosing interval of up to 12 weeks is considered intolerable, where HLX10 will be permanently discontinued and the subject should withdraw from the trial. For a treatment delay due to intolerance to HLX10 or placebo, chemotherapy should be administered as scheduled, and HLX10 or placebo may be postponed to the next cycle with no more than 12 weeks

	between doses; for a treatment delay due to intolerance to chemotherapy, chemotherapy may be postponed to the next cycle with an interval no more than 6 weeks.
Endpoints	**Primary Endpoint** • Progression free survival (PFS, assessed by IRRC according to RECIST v1.1) **Secondary Endpoints** • Overall survival (OS) • PFS (assessed by the investigator according to RECIST v1.1 and modified RECIST criteria) • Objective response rate (ORR, assessed by IRRC and investigator according to RECIST v1.1 criteria) • Duration of response (DOR, assessed by IRRC and investigator according to RECIST v1.1 criteria) • Incidence rates of AEs and SAEs • Pharmacokinetics (PK): serum HLX10 concentration • Immunogenicity evaluation: positive anti-drug antibody (ADA) • Relationship between PD-L1 expression level, MSI, TMB in tumor tissues and efficacy • Quality of life assessment
Inclusion/Exclusion Criteria	**Inclusion Criteria** 1. Voluntary participation in clinical studies; fully understand, be informed about the study and have signed the informed consent form (ICF); willingness to follow and ability to complete all trial procedures. 2. Aged ≥ 18 years and ≤ 75 years at the time of signing the ICF. 3. Histologically or cytologically diagnosed with ES-SCLC (according to the Veterans Administration Lung Study Group (VALG) staging system).

	4. No prior systemic therapy for ES-SCLC (including systemic chemotherapy, molecular targeted therapy, biological therapy, and other investigational therapies, etc.). 5. Patients who have received chemoradiotherapy for previous limited stage SCLC must be treated with curative intent and have a treatment-free interval of at least 6 months from the last course of chemotherapy, radiotherapy, or chemoradiotherapy to the diagnosis of extensive stage SCLC. 6. At least one measurable lesion as assessed by the IRRC according to RECIST v1.1 within 4 weeks prior to randomization. **Note: Measurable lesions mustnot be from previously irradiated sites. If the lesion at the previously irradiated site is the only selectable target lesion, anteroposterior images showing significant progression of the lesion should be provided by the investigator.** 7. Every effort should be made to provide tumor tissues that meet the requirements for the determination of PD-L1 expression level. Subjects are assessed for an evaluable PD-L1 expression category (negative, positive, or not available) by the central laboratory for randomization. **Note: It is recommended to provide formalin-fixed tumor tissue samples, paraffin-embedded tumor specimens (preferred), or FFPE tumor specimens or newly prepared unstained serial tissue sections (preferably adhesive slides) within 6 months prior to the first dose of study medication. A relevant pathology report must also be provided for the above specimens. Freshly collected specimens, radical resections, core needle biopsy, excisions, incisions, punch or clamp biopsies are acceptable (newly obtained tissues are preferred). Fine-needle aspirations (i.e., samples that lack a complete tissue structure and provide only cell suspension and/or cell smear), brush biopsies, and cell pellet samples from pleural or peritoneal effusions are**

unacceptable. For detailed requirements for tissue samples, see the laboratory manual.

8. Prior antineoplastic therapy must have been ≥ 2 weeks from the first dose in this study with treatment-related AEs resolved to NCI-CTCAE Grade ≤ 1 (except for Grade 2 alopecia).
9. An ECOG PS score of 0 or 1.
10. An expected survival ≥ 12 weeks.
11. Subjects with prior denosumab use that can and agree to switch to bisphosphonate therapy for bone metastases starting prior to randomization and throughout treatment;
12. Adequate major organ functions as defined by the following criteria (withoutblood transfusions, or treatment with albumin, recombinant human thrombopoietin or colony-stimulating factor (CSF) within 14 days prior to the first dose in this study):

Hematologic system	
Absolute neutrophil count (ANC)	≥ 1.5×10^9/L
Lymphocyte	≥ 0.5×10^9/L
Platelet (PLT)	≥ 100×10^9/L
Haemoglobin (Hb)	≥ 90 g/L
Liver function	
Total bilirubin (TBIL)	≤ 1.5×upper limit of normal (ULN) For patients with Gilbert's syndrome, total bilirubin ≤ 3 × ULN is acceptable
Alanine transaminase (ALT)	≤ 2.5×ULN; ≤ 5.0 × ULN for patients with liver metastases
Aspartic transaminase (AST)	≤ 2.5×ULN; ≤ 5.0 × ULN for patients with liver metastases
Alkaline phosphatase (ALP)	≤ 2.5×ULN; ≤ 5.0 × ULN for patients with liver or bone metastases
Renal function	
Creatinine (Cr)	≤ 1.5×ULN; In case of > 1.5 × ULN, creatinine clearance ≥ 50 mL/min

	(calculated from Cockcroft-Gault formula)
Coagulation function	
Activated partial prothrombin time (APTT)	≤ 1.5×ULN
International normalized ratio (INR)	≤ 1.5×ULN
The above requirements apply only to subjects who are not receiving anticoagulant therapy; subjects who are receiving anticoagulant therapy must maintain a stable dose of anticoagulants.	

13. Female patients must meet one of the following conditions:

① Menopause (defined as no menses for at least 1 year and no confirmed cause other than menopause), or

② Surgically sterilized (removal of the ovaries and/or uterus), or

③ With child-bearing potential, but must:

- have a negative serum pregnancy test within 7 days prior to the first dose of study drug, and
- agree to use contraception with an annual failure rate of < 1% or to remain abstinent (avoid heterosexual intercourse) from obtaining informed consent to at least 120 days after the last dose of trial medication and at least 150 days after the last dose of chemotherapy medication (Contraception methods with an annual failure rate of < 1% include bilateral tubal ligation, male sterilization, correct use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper-containing intrauterine devices), and
- not breastfeeding

14. Male patients must: agree to abstinence (avoid heterosexual intercourse) or take contraception measures as follows: male patients with a pregnant partner or a partner with childbearing potential must remain abstinent or use a condom to prevent embryonic exposure during chemotherapy treatment (carboplatin or etoposide) and for at least 150 days after the last dose of chemotherapy. Periodic abstinence (e.g., contraceptive methods based on calendar day, ovulation, basal body temperature or post-

	ovulation) and external ejaculation are ineligible methods of contraception. **Exclusion Criteria** 1. Histologically or cytologically confirmed mixed-type SCLC. 2. Other active malignancies within 5 years or at the same time. Localized tumors that have been cured, such as basal cell carcinoma, squamous-cell skin cancer, superficial bladder cancer, prostate carcinoma in situ, cervical cancer in situ and breast cancer in situ are acceptable. 3. Patients who are preparing for or have received an organ or bone marrow transplant. 4. Pleural or pericardial effusion requiring clinical intervention, or ascites. 5. Patients with known or documented active central nervous system (CNS) metastases and/or carcinomatous meningitis at screening. However, the following subjects are allowed to be enrolled: ① Subjects with asymptomatic brain metastases (i.e., no progressive central nervous system symptoms caused by brain metastases, no requirement for corticosteroids, and lesion size ≤ 1.5 cm) may be included, but are required to receive regular brain imaging as a site of lesion. ② Subjects with treated brain metastases which have been stable for at least 2 months (as confirmed by 2 radiological examinations at least 4 weeks apart after treatment of brain metastases), with no evidence of new or enlarging brain metastases, and with discontinued steroids 3 days prior to study drug administration. (Stable brain metastases here should be confirmed before the first dose of the study drug.) 6. Subjects with spinal cord compression that has not been radically treated with surgery and/or radiotherapy. 7. Patients with myocardial infarction within half a year before the first dose of the study drug, poorly controlled arrhythmia (including QTc intervals ≥ 450 ms for males and ≥ 470 ms for females) (QTc intervals are calculated

	by Fridericia's formula). 8. Class III to IV cardiac insufficiency according to NYHA classification or an LVEF (left ventricular ejection fraction) < 50% by cardiac color Doppler. 9. Subject has uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium > ULN). 10. Subject with peripheral neuropathy ≥ Grade 2 by CTCAE. 11. Human immunodeficiency virus (HIV) infection, , positive test for HIV antibody. 12. Active pulmonary tuberculosis. 13. Subjects with previous and concurrent interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonitis and severe impaired pulmonary function that may interfere with the detection and management of suspected drug-related pulmonary toxicity as judged by the investigator. 14. Hepatitis B (positive test for HBsAg or HBcAb and positive test for HBV-DNA) or Hepatitis C (positive tests for HCV antibody and HCV-RNA). Hepatitis B and C co-infection (positive test for HBsAg or HBcAb and positive test for HCV antibody); 15. Known active or suspected autoimmune or interstital lung diseases. Subjects in a stable state with no need for systemic immunosuppressant therapy are allowed to enroll. 16. Treatment with live vaccines within 28 days prior to study drug administration; inactivated viral vaccines for seasonal influenza are allowed. 17. Patients requiring treatment with systemic corticosteroids (> 10 mg/day prednisone efficacy dose) or other immunosuppressive drugs within 14 days prior to the first dose or during the study. However, in the absence of

	active autoimmune disease, subjects are allowed to use topical or inhaled steroids and adrenal hormone replacement therapy at doses equivalent to ≤ 10 mg/day of prednisone efficacy. 18. Any active infection requiring systemic anti-infective therapy within 14 days prior to study drug administration. 19. Major surgery within 28 days prior to the first dose of the study drug, defined as: surgeries requiring at least 3 weeks of recovery to be able to receive treatment in this study. 20. Radical radiation therapy within 3 months prior to study medications. **Note: Palliative radiotherapy to bone or palliative radiotherapy to superficial lesions is allowed according to local standards 14 days prior to the first dose. Radiotherapy covering more than 30% of the bone marrow area within 28 days prior to the first dose is not allowed.** 21. The subject has previously received other antibodies/drugs against immune checkpoints, such as PD-1, PD-L1, CTLA4, etc. 22. Participation in any other ongoing clinical studies, or less than 14 days from the end of the previous clinical study treatment to the start of this trial. 23. Known history of severe allergy to any monoclonal antibody. 24. Known hypersensitivity to carboplatin or etoposide. 25. Pregnant or lactating women. 26. Known history of psychotropics abuse or drug abuse. 27. In the judgment of the investigator, the subject has any other factors that may lead to a premature discontinuation.
Statistics	**Sample Size Estimation** The allocation ratio is 2:1 in this study. The sample size is estimated based on an assumption that the median progression-free survival (PFS) for placebo + chemotherapy (carboplatin-etoposide) is 5 months, and the hazard ratio (HR) for the HLX10 + chemotherapy arm versus the control arm is 0.7. At an overall significance level of $\alpha = 0.05$ (two-sided), and assuming an treatment period

of 24 months and an entire study period of 29 months, at least 336 PFS events are to be observed for an 85% power. Considering a dropout rate of 20%, a total of 489 subjects (326 in investigational arm and 163 in the control arm) need to be enrolled in the 2 arms.

Estimation of Blinded Sample Size

In this study, when 320 subjects are enrolled (accounting for about 2/3 of the planned enrollments), the sponsor will consider conducting a blinded sample size assessment. If the overall median PFS under the blind condition is lower than expected, the sponsor should communicate with the PI and regulatory authorities to increase the sample size (number of PFS events) as necessary.

Statistical Analysis Sets:

- Intent-to-Treat Set (ITT): defined as all subjects randomized into the trial. The ITT population will be the primary analysis population for the efficacy analysis in this study. ITT population will be analyzed based on treatment arms.
- Per Protocol Set (PPS): a subset of ITT, in which all randomized subjects who have received at least one post-treatment tumor assessment and have no major protocol deviation that significantly affects the primary efficacy are included. The analysis based on the PPS will serve as a support of ITT analyses.
- Safety Set (SS): defined as all subjects who received at least one dose of study drugs. The safety set is the primary population for safety endpoint analysis and will be analyzed based on treatment arms.
- Pharmacokinetic Set (PKS): including all subjects who have received at least one dose of HLX10, had at least one post-dose concentration measurement at scheduled PK time points, without any major protocol violation that could significantly affect the PK assessment. PKS will be used for PK analysis.

Efiicacy Analysis

- **Primary Efficacy Endpoint**

Progression-free survival (PFS): assessed by IRRC according to RECIST v1.1 criteria. PFS will be compared between the two arms using the stratified log-rank test with PD-L1 expression level (negative, positive, or not available), brain metastasis (yes versus no) and age (≥ 65 years versus < 65 years); HR and its 95% confidence interval are estimated by stratified COX proportional hazards model; medias is estimated using Kaplan Meier method and Kaplan-Meier curves are plotted.

- **Secondary Efficacy Endpoints**

➢ Overall survival (OS): using the same statistical method as the primary efficacy endpoint;

➢ Progression-free survival (PFS): as assessed by the investigator according to RECIST v1.1 and modified RECIST criteria and analyzed using the same method as the primary efficacy endpoint;

➢ Objective response rate (ORR): The stratified Cochran-Mantel-Haenszel (CMH) test is used for the difference in ORR between the two arms, and the odds ratio and its 95% confidence interval are estimated;

➢ Duration of response (DOR): the median is estimated using the Kaplan Meier method and Kaplan-Meier curves are plotted.

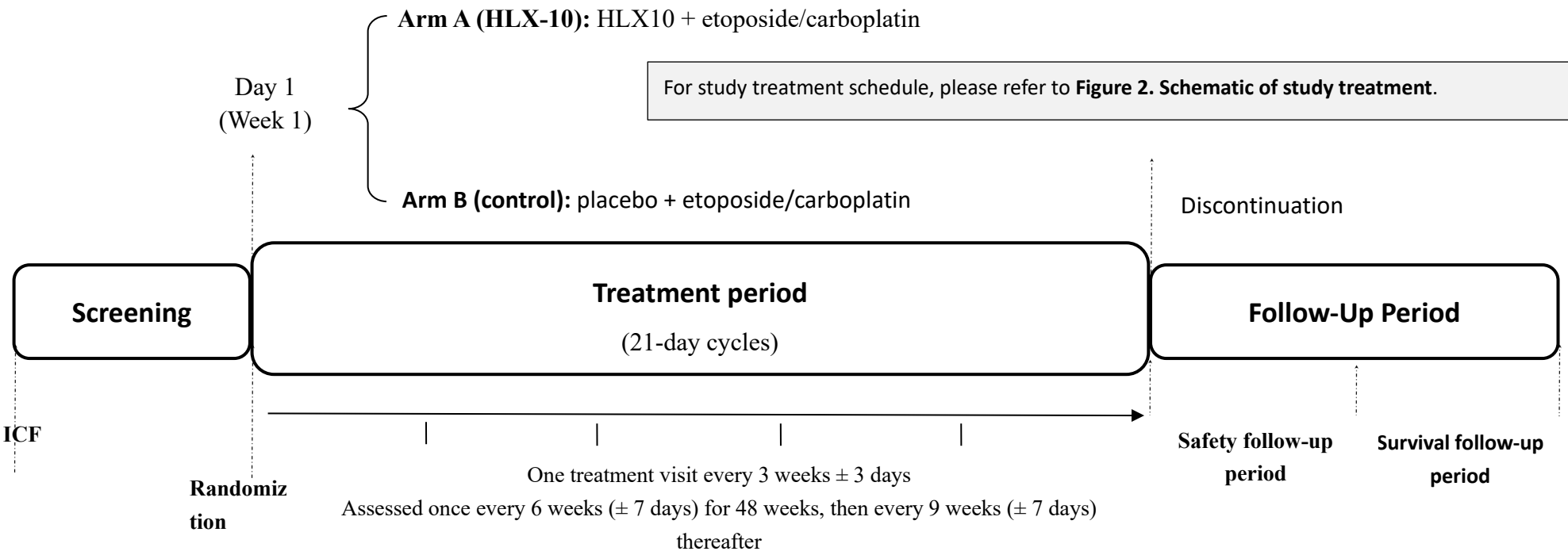
Interim Analysis:

An Independent Data Monitoring Committee (IDMC) will be established for this study to conduct the interim analysis. One interim analysis of PFS will be performed in this study. An α-spending function of O'Brien-Fleming type (approximated by the Lan-DeMets method) is used to control the overall type I error rate.

- The interim analysis of PFS is planned when 66% (approximately 222) of planned PFS events are observed, in which the safety and efficacy of the investigational product will be evaluated. The first interim analysis of PFS based on the O'Brien-Fleming alpha spending function had an alpha of 0.012 (two-sided).
- The final analysis of PFS will be performed when a target number of PFS events (approximately 336) are observed, and for final analysis the

	α is 0.046 (two-sided) based on the O'Brien-Fleming alpha spending function. **Safety Analysis** AEs will be described according to MedDRA terms and graded according to CTCAE v4.03. Adverse events occurring during or after the first dose of the study drug will be summarized by CTCAE grade. Treatment-emergent adverse events (TEAEs) and concomitant medications in the trial will be summarized separately by treatment arm. Laboratory measurements, ECOG, vital signs, physical examination and ECG will be summarized by treatment arm and visit. Values observed and changes from baseline will be descriptively reported by visit in this trial. **Pharmacokinetics and Immunogenicity** Serum drug concentration, pharmacokinetics, and ADA positive rates are descriptively summarized by visit.**Biomarker Analysis** At screening, the subjects' tumor tissues will be collected for determining PD-L1 expression level, microsatellite instability (MSI) and tumor mutation burden (TMB); the subjects' blood samples are collected for the detection of MSI and TMB. The primary objective is to assess the relationships between PD-L1 expression and MSI, TMB and efficacy. **Analysis of Subject-Reported Outcome Variables** Subjects' quality of life will be assessed by EQ-5D-5L scale, EORTC QLQ-C30 and EORTC QLQ-LC13 scale. Descriptive statistics are based on the allocation for the scale scores, subscale scores, and individual scores at each visit and their changes from baseline.

Figure 1. Overall study design



Stratification factors:

- Gender (male versus female)
- PD-L1 expression level (negative, positive, not available)
- Brain metastasis (yes versus no)
- Age (≥ 65 years versus < 65 years)

Screening period: At least 28 days

Safety follow-up period: 90 days after last dose. Safety visit is required at the site 30 days (±7 days) after the last dose, and telephone follow-up is required 90 days (±7 days) after the last dose.

Survival follow-up period: every 12 weeks ± 7 days

Study Procedures（1）

Periods	**Screening Period**		**Treatment Period (three-week cycles)**					**End-of-Treatment (EOT) visit[1]**	**Follow-Up Period[2]**	
Treatment Cycles/Visits	Screening Period		1	2	3	4	n	Discontinuation	Safety follow-ups	Survival follow-up[3]
Time of Visit	-28 to -8	-7 to -1	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after last dose (by telephone calls)	Every 12 weeks
Time Window[4]				± 3	± 3	± 3	± 3	+7	± 7	± 7
Management Procedures										
Informed consent form	**X**									
Inclusion/exclusion criteria	**X**									
Dispensing of subject ID card	**X**									
Demographics and medical history	**X**									
Prior and concomitant therapies[5]	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Clinical Operations/Assessments										
Adverse events[6]	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Quality of life[7]		**X**	**X**		**X**		**X**	**X**	**X**	
Echocardiography	**X**									
12-lead ECG	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Complete physical examination	**X**									
Symptom-directed physical examination			**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Height, weight and vital signs[8]	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	
ECOG scores		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Subsequent antineoplastic therapy									**X**	**X**
Survival status			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Study Procedures（2）

Periods	Screening Period		Treatment Period (three-week cycles)					End-of-Treatment (EOT) visit[1]	Follow-Up Period[2]	
Study Treatment										
Randomization[9]			X							
HLX10 or placebo[9]			X	X	X	X	X			
Etoposide + carboplatin			X	X	X	X				
Clinical Operations/Assessments: by study site										
Pregnancy test[10]		X			X		X	X	X	
Routine blood test, biochemistry, coagulation, urinalysis[11]		X	X	X	X	X	X	X	X	
T3 or FT3, T4 or FT4, TSH[12]		X			X		X	X	X	
HBV antibody, HBV DNA[13]	X									
● In case of HBV DNA (-) and: 1) HBsAg (+), or 2) HBcAb (+) and HBsAg (-) at baseline, HBV antibody and HBV DNA should be examined during the treatment period.					X		X	X	X	
HCV antibody, HCV RNA[13]	X									
● In case of HCV antibody (+) and HCV RNA (-)at baseline, HCV antibody and HCV RNA should be examined during the treatment period.					X		X	X	X	
HIV	X									
Clinical Operations/Assessments: by central laboratory										
HLX10-PK, ADA[14]			X	X		X	X	X	X	
Efficacy Assessment										
Radiological Examination[15]	X				X		X	X		
Biomarker Sample Collection										
Tumor tissue[16]	X									
Blood	X									

1. If a subject discontinues study treatment for any reason, an end-of-treatment (EOT) visit should be performed whenever possible and should be completed within 7 days after informed or discontinuation confirmed (and should be completed before the subject starts a new anti-tumor therapy);
2. All subjects are required to visit the study site for safety follow-up 30 days (± 7 days) after the last dose; if the end-of-treatment visit is delayed for any reasons and occurs after the time window of 30 days (± 7 days), no further safety follow-up visit is required. All subjects are required to receive a follow-up telephone call for safety follow-up 90 days (± 7 days) after the last administration. Only the information of AEs and AE-related concomitant drugs is collected. For subjects who discontinued for reasons other than disease progression, radiological assessments are to be continued as scheduled as far as possible, until disease progression, initiation of new antineoplastic therapy, withdrawal of ICF, death, or end of study, whichever occurs first.

Periods	Screening Period	Treatment Period (three-week cycles)	End-of-Treatment (EOT) visit[1]	Follow-Up Period[2]

3. Subjects should be followed for survival by telephone every 12 weeks ± 7 days after starting a new antineoplastic therapy or treatment termination criteria are met ; the frequency of survival follow-up may be increased as appropriate.
4. The maximum screening period is 28 days; the time windows are ± 3 days for treatment, ± 7 days for tumor assessment, + 7 days for EOT visit, and ± 7 days for follow-up. ECOG performance status, pregnancy test, blood routine, biochemistry, coagulation, urinalysis and thyroid function (T3 or FT3, T4 or FT4, TSH) should be completed within 7 days before randomization, and the subjects should meet the corresponding inclusion/exclusion criteria for enrollment.
5. All prior and concomitant medications are recorded from 30 days prior to signing the ICF through the safety follow-up visit; concomitant medications associated with AEs are recorded up to 90 days after the last study treatment.
6. All AEs and treatment emergent AEs are recorded from the time of signing the ICF until 90 days after the last study treatment. If a subject starts a new antineoplastic therapy during the AE collection period, only information on AEs related to study treatment are collected after the new antineoplastic therapy.
7. Quality of life scales including the EQ-5D-5L, the European Organization for Research and Treatment of Cancer Quality of Life Scale (EORTC QLQ-C30), and the European Organization for Research and Treatment of Cancer lung cancer questionnaire module (EORTC QLQ-LC13). Such scales are evaluated prior to the first dose and every other subsequent dosing cycle (i.e., pre-dose in Cycles 1, 3, 5, 7, etc.) until EOT. A quality of life assessment is required at the EOT visit if no assessment has been performed within the past 3 weeks. Re-assessments prior to dosing in Cycle 1 are not required for subjects who had a quality of life assessment on Day -7 to Day -1 of the screening period.
8. **The height measurement is performed only at screening**; vital signs include body temperature, pulse, respiratory rate, and blood pressure. Body weight is measured before each dose, and no dose adjustment of the study drug is required if the subject's body weight differs ≤ 10% from the reference value of the current dose during the study, otherwise the dose should be recalculated. This new body weight will serve as the baseline value for subsequent body weight measurements.
9. Study drug is administered on Day 1 of each 3-week cycle after all clinical and laboratory operations/assessments are completed. No more than 3 days must have elapsed between the date of randomization and the date of the first study dose.
10. Women of childbearing potential must have a serum pregnancy test. This is also performed within 3 days prior to dosing every other cycle during the treatment period.
11. Routine laboratory tests include routine blood test, coagulation, biochemistry and urinalysis. Routine blood test items include red blood cell count, hemoglobin, platelet, white blood cell count, white blood cell differential counts and percentages (including: basophils, eosinophils, lymphocytes, monocytes, neutrophils); biochemistry items include blood urea/urea nitrogen, creatinine, sodium, potassium, magnesium, chloride, carbon dioxide binding capacity or bicarbonate or total carbon dioxide, calcium, phosphorus, blood glucose, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase, total cholesterol, total protein, albumin; urinalysis items include specific gravity, pH, urine glucose, urine protein, ketone body and blood cells. These are performed **within 3 days before dose in each cycle**; for aforementioned laboratory tests scheduled on the same day as study treatment, the study treatment can be arranged only after the test results are obtained. For combined chemotherapy, routine blood tests should be performed on Day 8 (± 3 days) of each treatment cycle to closely monitor bone marrow suppression.
12. Thyroid function tests include triiodothyronine (T3 or FT3), thyroxine (T4 or FT4) and thyroid stimulating hormone (TSH) assays. This is also performed within 3 days prior to dosing every other cycle during the treatment period.
13. All subjects are tested for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody at screening; HBsAg positive subjects should be further tested for hepatitis B virus (HBV) DNA titer; and HCV antibody positive subjects should be further tested for HCV RNA. In case of HBV DNA (-) and: 1) HBsAg (+), or 2) HBcAb (+) and HBsAg (-) at baseline, HBV antibody and HBV DNA should be tested every 2 cycles during the treatment period. In case of HCV antibody (+) and HCV RNA (-) at baseline, HCV antibody and HCV RNA should be tested every 2 cycles during the treatment period.
14. PK and ADA sampling: (**Note: ADA samples will only be collected pre-dose** and procedures are described in the laboratory manual)
    - PK and ADA samples for HLX10 or placebo will be collected at the following time points: within 7 days **pre-dose** in Cycle 1, within 3 days **pre-dose** in Cycles 2, 4, 6, 8 and every 4 cycles thereafter, within 2 hours **after the end** of dosing in Cycles 1 and 8 of treatment period **(for PK only)**, at EOT visit and safety follow-up.
15. CT or MRI should be performed at screening, every 6 weeks (± 7 days) during the first 48 weeks after the start of study treatment, and every 9 weeks (± 7 days) after week 48 on sites including brain, chest, abdomen, pelvic cavity and any other sites suspected to have tumor lesions, in which **brain MRI or CT (preferably MRI) and bone scans** are required for all subjects at screening, and are performed in treatment period as determined by the investigator according to clinical needs; examination methods at the same site should be consistent as much as possible throughout the

Periods	Screening Period	Treatment Period (three-week cycles)	End-of-Treatment (EOT) visit[1]	Follow-Up Period[2]

study; if there are no contraindications, contrast agent should be used. The investigator and IRRC respectively assess the tumor images according to RECIST v1.1 (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation. If tumor assessment has been performed within 28 days prior to the first dose by the same methods and devices in the same hospital, it may serve as the baseline tumor assessment. At the EOT visit, if tumor imaging has been performed within the last 4 weeks, a re-test is not required. For subjects who discontinued for reasons other than disease progression, radiological assessments are to be continued as scheduled, until disease progression, initiation of new antineoplastic therapy, withdrawal of ICF, death, or end of study, whichever occurs first.

16. **To the extent possible**, formalin-fixed paraffin-embedded (FFPE) tumor samples (paraffin blocks or unstained sections) collected at or after the diagnosis of ES-SCLC and within 6 months prior to the start of study medication or pathological reports of such specimens should be provided. In case of no archived tumor tissue samples available, it is recommended to conduct a fresh tumor lesion biopsy at screening to obtain the corresponding tumor sample (the number of specimens required is based on the biopsy result). Tumor tissue sections will be used for immunohistochemical analysis to evaluate the expression level of PD-L1 in tumor cells and tumor-infiltrating immune cells and other purposes. Freshly collected specimens, radical resections, core needle biopsy, excisions, incisions, punch or clamp biopsies are acceptable. Fine-needle aspirations (i.e., samples that lack a complete tissue structure and provide only cell suspension and/or cell smear), brush biopsies, and cell pellet samples from pleural or peritoneal effusions are unacceptable. **For detailed requirements for tissue samples, see the laboratory manual.**

1 INTRODUCTION

1.1 Disease Background and Treatment Status

The global cancer statistics show that lung cancer is the most common cancer (11.6% of total cancer cases) and cause of death (18.4% of total cancer deaths) in the world. It is estimated that by 2018, 2.1 million new cases of lung cancer and 1.8 million new cases of lung cancer deaths will occur worldwide[1]. According to the data released by the National Cancer Center of China in 2018, there are about 781,000 new cases of lung cancer and 626,000 deaths from lung cancer each year in China, with the occurrence and mortality ranking first among malignant tumors[2].

Small cell lung cancer (SCLC) is derived from epithelial cells with neuroendocrine differentiation, accounting for 15%-20% of the total number of lung cancers[3]. The SCLC is staged using the US Veterans Administration (VA) staging system and is divided into a limited stage and an extensive stage. Most patients present with tumor metastases as the first symptom[4], and only 30% to 40% of patients are in the limited stage at the time of initial diagnosis[5]. Patients with extensive disease have shorter survival due to extensive tumor metastasis and poor physical status only with supportive care. The median survival time of untreated extensive small-cell lung cancer (ES-SCLC) is reported to be 2-4 months[6]. With a combination of surgery, radiotherapy and chemotherapy, the median survival of ES-SCLC patients can reach 8 to 13 months, with a 2-year survival rate of 5%[7].

Currently, systemic chemotherapy is still the primary treatment for ES-SCLC. The first-line platinum-based treatment recommended are the EP treatment (etoposide plus cisplatin), the EC treatment (etoposide plus carboplatin), the IP treatment (irinotecan plus cisplatin), and the IC treatment (irinotecan plus carboplatin). First-line treatment of SCLC is highly effective, but 80% of patients with limited-stage disease and almost all patients with extensive-stage disease relapse within one year, with a median survival of only 4 to 5 months after relapse[8]. Due to the limited understanding of SCLC genetic changes and the significant heterogeneity of SCLC at the genetic level, the success of some new treatment methods, such as intensive chemotherapy, supportive treatment, and molecular targeted therapy, did not benefit patients with extensive-stage SCLC. Therefore, there is an urgent need to explore more effective first-line treatments for extensive-stage SCLC.

1.2 Research Development and Basis for Dose Selection

1.2.1 Introduction to HLX10

HLX10 is an innovative monoclonal antibody targeting PD-1 independently developed by Shanghai Henlius Biotech, Inc. HLX10 is the IgG4 humanized monoclonal antibody. The gene sequence is screened using the hybridoma technique and genetically engineered to complete humanization. CHO were used as host cells to construct a stable cell line. The protein generated is composed of two identical heavy chains and two identical light chains linked by interchain disulfide bonds to form a typical human immunoglobulin IgG4 structure of a Y shape.

1.2.2 Non-clinical studies on HLX10

1.2.2.1 In vitro pharmacodynamic studies on HLX10

A series of in vitro pharmacodynamic studies comparing HLX10 with the positive control Nivolumab showed: HLX10 can bind to the surface of activated T cells expressing PD-1 and has the ability to block the binding of PD-1 to PD-L1 or PD-L2 on the cell surface. The binding and blocking ability of HLX10 present dose-dependence. The HLX10 in vitro mixed leukocyte reaction (MLR) assay showed that HLX10 blocks immunosuppression depending on the binding of PD-1 to its ligand, thereby stimulating activated CD4+ T cells, increasing T cell proliferation and producing more IL-2 cytokine. This phenomenon was dose-dependent in both the investigational product HLX10 and the positive control Nivolumab.

In addition, to investigate the occupancy ratio of HLX10 to PD-1 receptor on human T cells, different doses of HLX10 were used (50.0, 10.0, 2.0, 4.0×10^{-1}, 8.0×10^{-2}, 1.6×10^{-2}, 3.2×10^{-3} and 6.4×10^{-4} μg/mL) were pre-incubated with whole blood of six healthy subjects to simulate the injection of HLX10 into human blood. The results showed that with an increasing dose of HLX10 during pre-incubation, the PD-L1 receptor occupancy (RO) on $CD3^+$ T cells increased. In six healthy subjects, once the blood concentration of HLX10 in four of the subjects reached 2 μg/mL, the PD-1 receptor occupancy on CD3+ T cells reached more than 80%.

1.2.2.2 In vivo pharmacodynamic studies of HLX10

The results of anti-tumor efficacy and safety evaluation in NOD/SCID mice model subcutaneously xenografted with HT-29 human colon cancer cells showed that HLX10 had no adverse effects on the health status and body weight of mice in each dose group, indicating that HLX10 has a high level of safety. In terms of tumor suppressive effect, 30 mg/kg of HLX10 was able to effectively inhibit the growth of subcutaneously xenografted HT-29 human colon cancer cells in NOD/SCID mice in the presence of human peripheral blood mononuclear cells ($P < 0.0001$).

The anti-tumor effect and safety evaluation of human non-small cell lung cancer cells NCI-H292 in subcutaneous xenograft NOD/SCID mice showed that the higher dose of HLX10 did not cause adverse effects on the health status and body weight of mice, indicating that the investigational product HLX10 has a high level of safety. In terms of tumor suppression, HLX10 at a dose of 30 mg/kg significantly inhibited the growth of NCI-H292 tumor tissues in the presence of human peripheral blood mononuclear cells ($P < 0.001$), as compared with the placebo group in both tumor volume observation and statistical data.

In the dose exploration test (P16-106-TS), pharmacokinetic test (P16-106-YD) and chronic toxicity test (P16-106-CD), different doses of HLX10 were administered to cynomolgus monkeys to study the receptor occupancy (RO) at different time points before and after intravenous injection, which provided a basis for the selection of clinical effective dose and first dose.

The final results showed that the results of in vivo test were consistent with that of in vitro test in terms of the PD-1 receptor occupancy (RO) in human peripheral blood, i.e., once the HLX10 concentration in the blood of subjects reached 2 μg/mL, the occupancy rate of PD-1 receptor on CD3+ T cells reached more than 80%. In cynomolgus monkeys, when the blood concentrations of both test animals in the 3 mg/kg group were below the lower limit of detection (2 μg/mL), the corresponding RO values were still 79% and 97%, respectively. Taking all the results into consideration, it can be concluded that when a single dose of 3 mg/kg HLX10 was administered to cynomolgus monkeys, the RO saturation can be maintained for more than 4 weeks; when a dose of 5 mg/kg was administered continuously to cynomolgus monkeys for 13 weeks (once weekly), 100% RO saturation rate can be still achieved in some animals after the end of the 6-week recovery period. It can be inferred that HLX10 with lower clinical dose (less than 1 mg/kg) can reach RO saturation and show good curative effect.

1.2.2.3 Tissue cross reactivity of HLX10

The results of human tissue cross-reactivity study of HLX10 showed that HLX10-Biotin (2.0 μg/mL and 0.5 μg/mL) specifically bound to normal human lymphocytes, including lymphocytes in lymph node, lung, ileum, stomach, spleen, fallopian tube, colon and thymus tissues.

The results of cynomolgus monkey tissue cross-reactivity study of HLX10 showed that HLX10-Biotin (2.0 μg/mL and 0.5 μg/mL) specifically bound to normal cynomolgus monkey lymphocytes, including lymphocytes in stomach, jejunum, colon, spleen, thymus and mesenteric lymph nodes.

1.2.2.4 General pharmacology studies of HLX10

The general pharmacology evaluation test on central nervous system, cardiovascular system and respiratory system was conducted in cynomolgus monkeys. This test was conducted concomitantly with the chronic toxicity test. During the test, no test-related abnormalities were found in clinical symptoms of animals in each group, and no obvious abnormalities were found in their behaviors, breathing, etc. The abnormal findings of dying female animals in high-dose group euthanized on D55 were related to amoeba infection, while the abnormal findings of dead female animals on D64 were related to allergic reaction caused by drug administration. Surviving animals showed no regular changes in ECG parameters such as body temperature, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, blood oxygen saturation, heart rate, P-R, Q-T, and QTc intervals, and QRS duration. Therefore, when 5, 50, and 100 mg/kg of HLX10 were continuously given to cynomolgus monkeys via intravenous infusion for 13 weeks (once weekly), no significant effect on the central nervous system, cardiovascular system and respiratory system of cynomolgus monkeys was observed.

1.2.2.5 Acute toxicity study of HLX10

A 4-week dose exploration toxicity study was conducted in cynomolgus monkeys with repeated intravenous infusions of HLX10 at 5 mg/kg, 50 mg/kg, and 100 mg/kg, respectively. Administration was carried out on D1, D8, D15 and D22, and all animals were euthanized on D29 and subjected to gross anatomy. No dead or dying animal was seen during the test. One male animal in medium-dose

group had loose and soft stools on D15-20 and D21-29, respectively, and one female animal in medium-dose group also had loose stools on D11-13, D15-20 and D29, which was considered possibly related to the test sample. No abnormal symptoms related to the test sample was observed in the low-dose group and the high-dose group. No abnormal changes in body weight, food consumption, body temperature, ECG parameters, coagulation function indicators, blood biochemistry, or gross anatomy observations were observed in the animals in each dose group. The anti-drug antibodies (ADA) positive rates in 5, 50, and 100 mg/kg groups were 4/4, 3/4, and 4/4, respectively. The time of first appearance of antibodies was D8, and antibody titers ranged from < 1 to 128. Based on the results of this study, HLX10 was administered to cynomolgus monkeys for 4 weeks, and the animals were well tolerated to 100 mg/kg of HLX10. A dose of 100 mg/kg can be chosen for repeated-dose study with longer term.

1.2.2.6 Chronic toxicity study of HLX10

Toxicity and toxicokinetic studies were performed in cynomolgus monkeys with repeated intravenous infusions of HLX10 for 13 weeks and a recovery period of 6 weeks. Intravenous infusion of placebo and 5 mg/kg, 50 mg/kg, 100 mg/kg, respectively, of HLX10 were given once a week for a total of 13 weeks. During the study, no test sample-related death or dying situation was observed in animals in the low-dose and medium-dose groups. At the dose of 100 mg/kg, one female animal was found dead from a drug-related allergic reaction; one dying female animal was euthanized on D55 due to amoebic infection. The symptoms of loose stools and/or soft stools were observed in each dose group, and the occurrence in female animals of high-dose group (100 mg/kg) was slightly higher with slightly longer duration. The above gastrointestinal symptoms may be related to drug administration and are consistent with the adverse reactions of PD-1 reported. Except for two dead animals in the high-dose group, the gastrointestinal reactions (loose/soft stools) of the other animals recovered completely after the 6-week recovery period. Surviving animals in the treatment groups did not show any other abnormal symptoms related to the test sample during the study. Except for the female animal of high-dose group euthanized on D55, ADA positive state was observed in all animals of treatment groups, and ADA response was the highest in the low-dose group. Antibody titers increased with the increasing dose frequency and continued to increase until the end of the recovery period (D134). In combination

with toxicokinetic (TK) results, the presence of ADA significantly reduced systemic exposure in all dose groups. HLX10 at 5 and 50 mg/kg were repeatedly administered to cynomolgus monkeys via intravenous injection once weekly. No significant toxicity was observed after continuous administration for 13 weeks and no irritative reaction was seen at the infusion sites. No significant effect on major functional systems such as the cardiovascular system, central nervous system and respiratory system was observed. The maximum non-observed-adverse-effect level (NOAEL) of HLX10 was 50 mg/kg under the conditions of this experiment. The AUC_{last} and C_{max} of males on D85 were 597.60 h*mg/mL and 4909.72 μg/mL, respectively, and the AUC_{last} and C_{max} of females were 403.64 h*mg/mL and 3726.17 μg/mL, respectively.

1.2.2.7 Preclinical pharmacokinetic study of HLX10

The results of a pharmacokinetic study of HLX10 in cynomolgus monkeys by single intravenous infusion showed that after HLX10 was intravenously infused at 3, 10 and 30 mg/kg in animals, blood drug concentrations all increased with increasing dose. The systemic exposure (C_{max} and AUC_{last}) increased with the increasing dose. The median resorting time (MRT) was between 153.02-231.28 h. The elimination half life ($t_{1/2}$) was between 137.97-256.99 h. The results showed that in the dose range of 3-30 mg/kg, the test sample basically showed linear pharmacokinetic profile in cynomolgus monkeys. The clearance rate among groups and volume of distribution (Vz) of HLX10 among groups were similar, which ranged in 0.13-0.23 mL/h/kg and 38.05-53.52 mL/kg, respectively. All animals in HLX10 dose groups at 3, 10 and 30 mg/kg on D8, D15, D22 and D29 were positive for anti-drug antibody (ADA), the time of first appearance of antibody was on D8, and the antibody titer ranged from < 1 to 512. Except that the area under the concentration-time curve (AUC_{last}, AUC_{inf}) of female animals in 10 mg/kg group was lower than that of male animals with statistical difference ($p < 0.05$), there was no significant difference in pharmacokinetic parameters between genders in other dose groups. According to the analysis results of antibody generation, it can be concluded that 2/3 female animals in 10 mg/kg group developed strong antibody on D22, with antibody titers of 8-128, resulting in female animals having slightly faster elimination and lower area under curve (AUC_{last}, AUC_{inf}) than male animals.

1.2.2.8 Toxicokinetics study of HLX10

The toxicokinetic study was conducted concomitantly with the 4-week dose exploration toxicity test of repeated HLX10 intravenous infusions to cynomolgus monkeys. The results showed that, on D1 and D22, the systemic exposure of HLX10 (C_{max} and AUC_{last}) increased with the increasing dose. The generation of anti-drug antibodies in some animals on D22 accelerated the elimination of blood HLX10 concentration. In ADA-negative animals, the mean C_{max} and mean AUC_{last} in each dose group on D22 were higher than those on D1, indicating that the drug accumulated to some extent. The blood HLX10 concentration in the D22 pre-dose samples also showed this feature. The accumulation factor was between 2.24-2.41. Compared with those on D1, the ADA negative group showed a smaller volume of distribution of HLX10 and a slower clearance rate on D22. In the ADA-positive group, the clearance increased significantly.

The toxicity and toxicokinetic studies of repeated HLX10 intravenous infusions in cynomolgus monkeys for 13 weeks and a 6-week recovery period were conducted concomitantly with a toxicokinetic study. The results showed that on D1 and D85, the systemic exposure of HLX10 (C_{max} and AUC_{last}) increased with the increasing dose, and dose-dependent toxicokinetic characteristics were presented. Some of the animals generated anti-drug antibodies after repeated administration. In ADA-negative animals, the mean C_{max} and mean AUC_{last} in each dose group on D85 were higher than those on D1, indicating that drug accumulation was present. The blood HLX10 concentration in the D85 pre-dose samples also showed this feature. The accumulation factor was between 2.34–4.32. Compared with those on D1, the ADA negative group showed a smaller volume of distribution of HLX10 and a slower clearance rate on D85. In the ADA-positive group, the clearance increased significantly. On D1, male animals in the 100 mg/kg group had slightly higher systemic exposure (AUC_{last}, AUC_{inf}) and slightly lower clearance (CL) than female animals. There was no significant gender difference in the pharmacokinetic parameters on D1 and D85 in other groups.

1.2.2.9 HLX10 immunogenicity and immunotoxicity

Evaluation tests for immunogenicity and immunotoxicity were carried out in cynomolgus monkeys, and this test was conducted concomitantly with the chronic toxicity study. The results showed that when 5, 50, and 100 mg/kg of HLX10 were administered intravenously to cynomolgus monkeys once

a week for 13 weeks, no immunotoxicity was observed at dose of 5 and 50 mg/kg. At the dose of 100 mg/kg, one female died from an allergic reaction, the anti-drug antibody was positive, and IL-6 increased after the drug administered. The CD3+, CD4+ and CD4+/CD8+ ratio decreased in male animals at 100 mg/kg, while CD8+ increased and the increase was associated with the pharmacological activity of the test sample. Anti-drug antibodies could be seen after HLX10 was administered to animals. The occurrence of anti-drug antibodies in the low-dose group was higher than that in the medium- and the high-dose group. Antibody titer increased with the increase of administration time, and could lead to significant reduction of system exposure. As a humanized antibody, HLX10 is an exogenous substance to cynomolgus monkeys. Therefore, immunogenicity in the animals is reasonable. For immunogenicity evaluation of antibody-based drugs, human clinical trial is a preferred method.

1.2.2.10 Other preclinical studies of HLX10

The hemolysis study of HLX10 showed that HLX10 at a concentration of 10 mg/mL had no hemolytic effect on human red blood cells in vitro and did not cause red blood cell aggregation.

The local irritation study was conducted concomitantly with the chronic toxicity test. The test results showed that when HLX10 at doses of 5, 50 and 100 mg/kg were administered to cynomolgus monkeys by repeated intravenous infusion once weekly for 13 weeks, no obvious irritative injury was seen in blood vessels and surrounding tissues in infusion sites in the dose range of 0.5-10.0 mg/mL.

No genotoxicity study of HLX10 has been conducted yet.

1.2.3 Clinical studies of HLX10

HLX10 has been approved by the US FDA, China Taiwan FDA and China NMPA for a dose escalation phase I clinical trial. There are four dose groups (0.3, 1, 3 and 10 mg/kg, once two weeks) in the trial, with a maximum enrollment of about 30 subjects. At present, three patients in the fourth dose group have completed the enrollment, and no dose-limiting toxicity was observed in all dose groups during the dose-limiting toxicity observation period.

1.2.4 Basis for selection of chemotherapy as a control group

The platinum-based chemotherapy provided in this study is EC regimen (etoposide plus carboplatin), which is the first-line chemotherapy regimen for ES-SCLC recommended by NCCN and Chinese Expert Consensus on the Diagnosis and Treatment of Advanced Primary Lung Cancer (2016 Edition), allowing investigators and subjects to have more flexibility in conducting study and treatment according to the standard clinical practice of drugs.

1.2.5 Basis for combined treatment

With the deepening of the study on the molecular pathogenesis of cancer, the immunological mechanism of tumorigenesis and development has gradually become a study hotspot. It is becoming increasingly clear that cancer can be recognized by the immune system, and in some cases, the immune system can control or even eliminate tumors. PD-1 was originally cloned by Ishida et al.[9] as a member of the CD28 superfamily in murine T cell hybridomas. It is a monomeric glycoprotein that is mainly expressed on the surface of activated macrophages, T lymphocytes, B lymphocytes, NK cells, and some myeloid cells. Its ligands, PD-L1 (programmed death ligand 1) and PD-L2, are mainly expressed on tumor cells and antigen-presenting cells[10][11][12]. Because activation of the PD-1 gene may be involved in the classical type of programmed cell death, it is named programmed death receptor 1 (PD-L1). PD-L1 is highly expressed in a variety of cancers, and is as high as 88% in some cancers. In these cancers (including lung cancer), PD-1 binds to PD-L1 in tumor tissues, weakens the body's immune response, protects tumor tissues from cytotoxic T cells, and leads to tumor immune tolerance[13][14]. Therefore, T cell anti-tumor response can be enhanced by blocking the binding of PD-1 to its ligand PD-L1[15][16][17][18][19].

In recent years, with the rapid development of tumor immunotherapy, the focus of first-line treatment for advanced NSCLC with no driver gene has gradually turned to immunotherapy, and multiple PD-1 inhibitors have been approved by the FDA for NSCLC treatment; The National Comprehensive Cancer Network (NCCN) Guidelines have also included PD-1 inhibitors as one of the recommended protocols for the treatment of relapsed SCLC. In the absence of breakthrough of targeted drug treatment for SCLC in the past 30 years, a new drug has been discovered for SCLC. In 2018, the FDA approved Nivolumab for the treatment of relapsed SCLC. In addition, a number of clinical trials of PD-1

antibody combined with chemotherapy for SCLC are currently underway. Preliminary results show that PD-1 inhibitor plus chemotherapy can significantly improve overall survival and progression-free survival, and is expected to become the new standard of first-line treatment for SCLC.

The survival of cytotoxic chemotherapy in patients with ES-SCLC reaches a plateau, leaving much room for improving the prognosis of such patients. Exposure of the immune system to high levels of tumor antigens can reasonably be expected to result in cytotoxicity effects on tumor cell (TC) by cytotoxic chemotherapy, and restoration of tumor-specific T cell immunity in this setting may produce deeper and durable responses than standard chemotherapy alone by inhibiting the PD-L1/PD-1 signaling pathway[20][21]. Therefore, it is reasonable to assume that the combination of immunosuppressive and cytotoxic chemotherapy drugs may have a stronger synergistic anti-tumor effect.

1.2.6 Basis for HLX10 dose selection

Based on the results of the HLX10 preclinical and phase I clinical trials, the currently available PK and ADA data support an average body weight dose of HLX10 of 4.5 mg/kg administered every 21 days as the recommended dose for phase III clinical studies.

1.3 Assessment for Risks and Benefits

1.3.1 Potential benefits

Atezolizumab (trade name Tecentriq), a PD-L1 inhibitor developed by Roche in September 2018, has achieved landmark results in the first-line treatment of SCLC:

IMpower 133, a randomized, controlled phase III study evaluating atezolizumab plus carboplatin-etoposide versus placebo plus carboplatin-etoposide in the treatment of untreated extensive SCLC, enrolled 403 patients and randomized at 1:1 with a median follow-up of 13.9 months. Median overall survival were 12.3 months (95% confidence interval (CI), 10.8-15.9) in the atezolizumab plus chemotherapy group and 10.3 months (95% CI, 9.3-11.3) in the placebo plus chemotherapy group (HR = 0.70, 95% CI 0.54-0.91, P = 0.007). Median progression-free survival was 5.2 months (95% CI, 4.4-5.6) in the atezolizumab plus chemotherapy group and 4.3 months (95% CI, 4.2-4.5) in the

placebo plus chemotherapy group (HR = 0.77, 95% CI 0.62-0.96, P = 0.02). At the same time, in terms of safety, the safety of Atezolizumab plus chemotherapy was consistent with that in the previous reports and no new toxicity was found.

Based on the above study results, Henlius plans to study the anti-tumor activity of HLX10 plus chemotherapy as first-line treatment of ES-SCLC. The preliminary efficacy, safety and tolerability data of PD-L1 plus chemotherapy in the IMpower 133 study supports the use of this treatment in ES-SCLC. The primary objective of this phase III study is to determine the clinical efficacy and safety of HLX10 plus chemotherapy in previously untreated ES-SCLC patients.

1.3.2 Identified and potential risks

PD-1/PD-L1 inhibitors not only enhance the anti-tumor effect of cellular immunity, but could also enhance the normal immune response, leading to immune tolerance imbalance and immune-related adverse reactions (irAEs). IrAEs can affect any organ in the human body, and nearly two-thirds of patients currently treated with immune checkpoint inhibitors experience irAEs of varying degrees[20,21]. In February 2018, NCCN and ASCO jointly issued the Guidelines for the Management of Toxicity Related to Immunotherapy (Version 1, 2018), which states that the immune-related adverse events of the skin, intestine, endocrine, lung and musculoskeletal systems are relatively common, while the immune-related adverse events of the cardiovascular, hematological, renal, neurological and ophthalmic systems are rare. Most immune-related adverse events were mild-moderate in severity; common irAEs known in patients currently treated with PD-1/PD-L1 inhibitors were as follows: skin toxicity (mainly maculopapular rash and pruritus; 30% to 40%), diarrhea and/or colitis (8% to 19%), fatigue (16% to 24%), immune-related hepatitis (5%), hypothyroidism (4% to 10%), hyperthyroidism (4%), hypophysitis (< 1%), type 1 diabetes, immune-related pneumonia, sarcoidosis, inflammatory arthritis, etc. Others such as cardiovascular adverse events, anemia, thrombocytopenia, nephritis, encephalopathy, leukoencephalopathy, post-reversible encephalopathy syndrome (PRES), peripheral motor and sensory neuropathy, uveitis, episcleritis, blepharitis, and acute pancreatitis occurred less frequently.

The safety evaluation of IMpower 133 in ES-SCLC also showed that the occurrences of AEs in the atezolizumab + EC group and placebo + EC group were comparable, with the occurrences of AEs of

any grade being 100% and 96.4% in the two groups, respectively; the occurrences of grade 3-4 AEs were 67.2% and 63.8% in the two groups, respectively. The occurrences of treatment-related AEs were 94.9% and 92.3%, respectively. The occurrences of SAEs were 37.4% and 34.7%, respectively; the occurrences of immune-related AEs were 39.9% and 24.5%, respectively. The comparisons for occurrences of most common grade 3-4 AEs: Neutropenia (22.7% and 24.5%), anemia (14.1% and 12.2%), neutrophil count decrease (14.1% and 16.8%), thrombocytopenia (10.1% and 7.7%), leukopenia (5.1% and 4.1%). The occurrences of immune-related grade 3-4 AEs in the atezolizumab + EP group were 2% for rash, 1.5% for hepatitis, 2% for infusion-related reactions, and 0.5% for pneumonia.

1.3.3 Overall benefits: risk and ethical assessment

At present, chemotherapy for advanced SCLC has encountered the bottleneck of efficacy, and it is urgent to explore more effective first-line treatment for SCLC. With the progress of various studies, immune checkpoint combination therapy has become a new treatment option for SCLC, which is likely to greatly improve the prognosis of SCLC patients. At the same time, the adverse events of the atezolizumab combination protocol were consistent with the known toxicity of monotherapy, and no new safety signals were found. No DLT was observed based on the current first-in-human study data for HLX10, and the available safety data and pharmacokinetic data demonstrate that the safety of HLX10 in patients is acceptable enough to support the implementation of this phase of the clinical study.

2 OBJECTIVES

2.1 Primary Objective

To evaluate the clinical efficacy of HLX10 combining with chemotherapy versus placebo combining with chemotherapy in previously untreated patients with ES-SCLC.

2.2 Secondary Objective

To evaluate the safety and tolerability of HLX10 combining with chemotherapy versus placebo

combining with chemotherapy in previously untreated patients with ES-SCLC.

3 STUDY PROTOCOL

3.1 Overall Study Design

This is a randomized, double-blind, placebo-controlled, multicenter, clinical Phase III study to evaluate the clinical efficacy, safety and tolerability of recombinant humanized anti-PD-1 monoclonal antibody injection (HLX10) or placebo in combination with chemotherapy in patients with previously untreated ES-SCLC, to collect PK parameters and to investigate the biomarker related to efficacy. For details, please refer to Figure 1 "Overall study design" and study events flow chart.

3.2 Endpoints

3.2.1 Primary endpoint

- Progression free survival (PFS, assessed by IRRC according to RECIST v1.1)

3.2.2 Secondary endpoints

- Overall survival (OS)
- PFS (assessed by the investigator according to RECIST v1.1 and modified RECIST criteria)
- Objective response rate (ORR, assessed by IRRC and the investigator according to RECIST v1.1 criteria)
- Duration of response (DOR, assessed by IRRC and the investigator according to RECIST v1.1 criteria)
- Incidence rates of AEs and SAEs
- Pharmacokinetics (PK): serum HLX10 concentration
- Immunogenicity evaluation: positive anti-drug antibody (ADA) rate
- Relationship between PD-L1 expression level, MSI, TMB in tumor tissues and efficacy
- Quality of life assessment

3.3 Randomization, Blinding, and Unblinding

A randomized, double-blind design is employed in this trial. Eligible subjects are randomly allocated to the following two arms using an interactive web/voice response system (IWRS/IVRS) at 2:1 ratio:

- Arm A (HLX10): HLX10 + chemotherapy (carboplatin-etoposide)
- Arm B (control): placebo + chemotherapy (carboplatin-etoposide)

Randomization are stratified by: PD-L1 expression level (negative, positive, not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years). During the study, the subjects, the investigator, the sponsor, and the designees are not aware of the randomized allocation, except in the event of emergency unblinding.

During the course of treatment with the study drug, if the investigator determines that the study drug is related to a life-threatening situation of the subject, and the investigator considers that knowing the medication of the subject is conducive to the handling of adverse events, an emergency unblinding is allowed. The decision to unblind in an emergency is the responsibility of the investigator and will not be delayed or declined by the sponsor; however, the investigator may contact the sponsor or its designees to discuss the unblinding and the protocol that is in the best interest of the subject prior to unblinding. The investigator shall ensure that unblinding is performed in strict accordance with the protocol. The investigator shall inform the sponsor of the circumstances of and reasons for emergency unblinding as soon as possible, and record these details clearly on the subject's source document. The unblinding process is completed on the IWRS using individual emergency unblinding identification numbers. If deemed necessary, the unblinding shall only apply to the affected subject.

The study will be unblinded overall after the last subject completed the study visit. The study shall remain blinded unless there is an emergency medical condition (emergency treatment is only possible when being informed of the randomized medication) or unblinding is requested by the regulatory authorities. Only when all data have been input into the database, all data queries have been resolved and subjects have been allocated into analysis sets, can the random codes be unblinded.

3.4 Number of Subjects

489 subjects are to be enrolled in study in a randomization ratio of 2:1, with 326 in the HLX10 arm

and 163 in the placebo arm.

3.5 Eligibility

3.5.1 Inclusion criteria

1. Voluntary participation in clinical studies; fully understand, be informed about the study and have signed the informed consent form (ICF); willingness to follow and ability to complete all trial procedures.
2. Aged ≥ 18 years and ≤ 75 years at the time of signing the ICF.
3. Histologically or cytologically diagnosed with ES-SCLC (according to the Veterans Administration Lung Study Group (VALG) staging system).
4. No prior systemic therapy for ES-SCLC (including systemic chemotherapy, molecular targeted therapy, biological therapy, and other investigational therapies, etc.).
5. Patients who have received chemoradiotherapy for previous limited stage SCLC must be treated with curative intent and have a treatment-free interval of at least 6 months from the last course of chemotherapy, radiotherapy, or chemoradiotherapy to the diagnosis of extensive stage SCLC.
6. At least one measurable lesion as assessed by the IRRC according to RECIST v1.1 within 4 weeks prior to randomization.

   Note: Measurable lesions are not from previously irradiated sites. If the lesion at the previously irradiated site is the only selectable target lesion, anteroposterior images showing significant progression of the lesion should be provided by the investigator.
7. Every effort should be made to provide tumor tissues that meet the requirements for the determination of PD-L1 expression levels. Subjects are assessed for an evaluable PD-L1 expression category (negative, positive, or not available) by the central laboratory for randomization.

   Note: It is recommended to provide formalin-fixed tumor tissue samples, paraffin-embedded tumor specimens (preferred), FFPE tumor specimens or newly prepared unstained serial tissue sections (preferably adhesive slides) within 6 months prior to the first dose of study medication. A relevant pathology report must also be provided for the above

specimens. Freshly collected specimens, radical resections, core needle biopsy, excisions, incisions, punch or clamp biopsies are acceptable (newly obtained tissues are preferred). Fine-needle aspirations (i.e., samples that lack a complete tissue structure and provide only cell suspension and/or cell smear), brush biopsies, and cell pellet samples from pleural or peritoneal effusions are unacceptable. For detailed requirements for tissue samples, see the laboratory manual.

8. Prior antineoplastic therapy must have been ≥ 2 weeks from the first dose in this study with treatment-related AEs resolved to NCI-CTCAE Grade ≤ 1 (except for Grade 2 alopecia).
9. An ECOG PS score of 0 or 1
10. An expected survival ≥ 12 weeks.
11. Subjects with prior denosumab use that can and agree to switch to bisphosphonate therapy for bone metastases starting prior to randomization and throughout treatment;
12. Normal major organ functions as defined by the following criteria (no blood transfusions, or treatment with albumin, recombinant human thrombopoietin or colony-stimulating factor (CSF) within 14 days prior to the first dose in this study):

Hematologic system	
Absolute neutrophil count (ANC)	≥ 1.5×10^9/L
Lymphocyte	≥ 0.5×10^9/L
Platelet (PLT)	≥ 100×10^9/L
Haemoglobin (Hb)	≥ 90 g/L
Liver function	
Total bilirubin (TBIL)	≤ 1.5×upper limit of normal (ULN) For patients with Gilbert's syndrome, total bilirubin ≤ 3 × ULN is acceptable
Alanine transaminase (ALT)	≤ 2.5×ULN; ≤ 5 × ULN for patients with liver metastases
Aspartic transaminase (AST)	≤ 2.5×ULN; ≤ 5 × ULN for patients with liver metastases
Alkaline phosphatase (ALP)	≤ 2.5×ULN; ≤ 5.0 × ULN for patients with liver or bone metastases
Renal function	
Creatinine (Cr)	≤ 1.5×ULN; In case of > 1.5 × ULN, creatinine clearance ≥ 50 mL/min (calculated from Cockcroft-Gault formula)

Coagulation function	
Activated partial prothrombin time (APTT)	≤ 1.5×ULN
International normalized ratio (INR)	≤ 1.5×ULN
The above requirements apply only to subjects who are not receiving anticoagulant therapy; subjects who are receiving anticoagulant therapy must maintain a stable dose of anticoagulants.	

13. Female patients must meet one of the following conditions:

① Menopause (defined as no menses for at least 1 year and no confirmed cause other than menopause), or

② Surgically sterilized (removal of the ovaries and/or uterus), or

③ With child-bearing potential, but must:

- have a negative serum pregnancy test within 7 days prior to first dose, and
- agree to use contraception with an annual failure rate of < 1% or to remain abstinent (avoid heterosexual intercourse) from obtaining informed consent to at least 120 days after the last dose of trial medication and at least 150 days after the last dose of chemotherapy medication (Contraception methods with an annual failure rate of < 1% include bilateral tubal ligation, male sterilization, correct use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper-containing intrauterine devices), and
- not breastfeed

14. Male patients must: agree to abstinence (avoid heterosexual intercourse) or take contraception measures as follows: male patients with a pregnant partner or a partner with childbearing potential must remain abstinent or use a condom to prevent embryonic exposure during chemotherapy treatment (carboplatin or etoposide) and for at least 150 days after the last dose of chemotherapy. Periodic abstinence (e.g., contraceptive methods based on calendar day, ovulation, basal body temperature or post-ovulation) and external ejaculation are ineligible methods of contraception.

3.5.2 Exclusion criteria

1. Histologically or cytologically confirmed mixed SCLC.

2. Other active malignancies within 5 years or at the same time. Localized tumors that have been cured, such as basal cell carcinoma, squamous-cell skin cancer, superficial bladder cancer, prostate carcinoma in situ, cervical cancer in situ and breast cancer in situ are acceptable.
3. Patients who are preparing for or have received an organ or bone marrow transplant.
4. Pleural or pericardial effusion requiring clinical intervention, or ascites.
5. Patients with known or documented active central nervous system (CNS) metastases and/or carcinomatous meningitis at screening. However, the following subjects are allowed to be enrolled: 1) Subjects with asymptomatic brain metastases (i.e., no progressive central nervous system symptoms caused by brain metastases, no requirement for corticosteroids, and lesion size ≤ 1.5 cm) may be included, but are required to receive regular brain imaging as a site of lesion. 2) Subjects with treated brain metastases which have been stable for at least 2 months (as confirmed by 2 radiological examinations at least 4 weeks apart after treatment of brain metastases), with no evidence of new or enlarging brain metastases, and with discontinued steroids 3 days prior to study drug administration. (Stable brain metastases here should be confirmed before the first dose of the study drug.)
6. Subjects with spinal cord compression that has not been radically treated with surgery and/or radiotherapy.
7. Patients with myocardial infarction within half a year before the first dose of the study drug, poorly controlled arrhythmia (including QTc intervals ≥ 450 ms for males and ≥ 470 ms for females) (QTc intervals are calculated by Fridericia's formula).
8. Class III to IV cardiac insufficiency according to NYHA classification or an LVEF (left ventricular ejection fraction) < 50% by cardiac color Doppler.
9. Subject has uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium > ULN).
10. Subject with peripheral neuropathy ≥ Grade 2 by CTCAE.
11. Human immunodeficiency virus (HIV) infection, positive test for HIV antibody.
12. Active pulmonary tuberculosis.
13. Subjects with previous and concurrent interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonitis and severe impaired pulmonary function that may

interfere with the detection and management of suspected drug-related pulmonary toxicity as judged by the investigator.

14. Hepatitis B (positive test for HBsAg or HBcAb and positive test for HBV-DNA) or Hepatitis C (positive tests for HCV antibody and HCV-RNA). Hepatitis B and C co-infection (positive test for HBsAg or HBcAb and positive test for HCV antibody);
15. Known active or suspected autoimmune diseases. Subjects in a stable state with no need for systemic immunosuppressant therapy are allowed to enroll.
16. Treatment with live vaccines within 28 days prior to study drug administration; inactivated viral vaccines for seasonal influenza are allowed.
17. Subjects requiring treatment with systemic corticosteroids (> 10 mg/day prednisone efficacy dose) or other immunosuppressive drugs within 14 days prior to the first dose or during the study. However, in the absence of active autoimmune disease, subjects are allowed to use topical or inhaled steroids and adrenal hormone replacement therapy at doses equivalent to ≤ 10 mg/day of prednisone efficacy.
18. Any active infection requiring systemic anti-infective therapy within 14 days prior to study drug administration.
19. Major surgery within 28 days prior to the first dose of the study drug, defined as: surgeries requiring at least 3 weeks of recovery to be able to receive treatment in this study.
20. Radical radiation therapy within 3 months prior to study medications.

Note: Palliative radiotherapy to bone or palliative radiotherapy to superficial lesions is allowed according to local standards 14 days prior to the first dose. Radiotherapy covering more than 30% of the bone marrow area within 28 days prior to the first dose is not allowed.

21. The subject has previously received other antibodies/drugs against immune checkpoints, such as PD-1, PD-L1, CTLA4, etc.
22. Participation in any other ongoing clinical studies, or less than 14 days from the end of the previous clinical study treatment to the start of this trial.
23. Known history of severe allergy to any monoclonal antibody.
24. Known hypersensitivity to carboplatin or etoposide.
25. Pregnant or lactating women.
26. Known history of psychotropics abuse or drug abuse.

27. In the judgment of the investigator, the subject has any other factors that may lead to a premature discontinuation.

3.5.3 Criteria for discontinuation

3.5.3.1 Reasons for premature discontinuation

A discontinuation of treatment means that the subject will no longer receive a study medication of this trial. Reasons for the discontinuation of treatment may include:

1. Poor compliance that has affected the efficacy and safety evaluation;
2. AEs or SAEs that are inappropriate to continue the study treatment as judged by the investigator;
3. Evidence of unequivocal progression or worsening of the disease;
4. A delayed dosing of the study drug meeting the criteria in Section 3.6.3;
5. Loss to follow-up or death;
6. Withdrawal of informed consent;
7. Other reasons of discontinuation as determined by the investigator in the best interest of the subject.

3.5.3.2 Management of premature discontinuations

The reasons for premature discontinuations shall be documented in the eCRF.

All subjects who discontinue the trial prematurely shall undergo an EOT visit and be followed up for safety.

Subjects who discontinue the trial for reasons other than disease progression should be radiologically followed up until disease progression, withdrawal of informed consent, death or start of a new antineoplastic therapy.

All AEs present at the time of discontinuation must be followed up until the outcomes of such adverse events.

In case of an enrolled subject's withdrawal for any reasons, no subject replacement is permitted.

3.6 Early Termination of Study/Closure of Study Site

The study may be terminated prematurely due to the following reasons. Written permissions of both the principal investigator and the sponsor are required for the early termination of the study, and results of the study shall be reported in accordance with the requirements of the protocol.

1. The study is unlikely to be completed within an acceptable time frame due to difficulties in subject enrollment;
2. The investigator questions the safety of the drug during the study and concludes that further study would pose serious risks to the subjects;
3. The principal investigator and the sponsor believe that the number and severity of adverse events suggest a premature termination;
4. The efficacy fails to meet expectations and it is not necessary to continue the clinical trial;
5. The study is revoked by regulatory authorities;
6. The sponsor has the right to terminate the study at a certain study site in the event of:

- serious violations of ICH-GCP by the study site;
- repeated serious protocol violations by the study site;

Upon the termination of the study, all related records shall be kept for future reference.

3.7 Study Treatment

3.7.1 Information on study drugs

Investigational product HLX10

Name	Recombinant humanized anti-PD-1 monoclonal antibody injection (HLX10)
Specification	HLX10 100 mg/10 mL/vial
Storage condition	2–8 °C
Manufacturer	Shanghai Henlius Biotech, Inc.
Supplier	Shanghai Henlius Biotech, Inc.

Placebo control

A visually indistinguishable injection without active ingredient of HLX10.

Other study medications

Commercially available carboplatin and etoposide supplied by Shanghai Henlius Biotech, Inc.

Kindly refer to the currently approved prescribing information for information on formulation, preparation, storage and administration of carboplatin and etoposide.

3.7.2 Route of administration and dosage

Study drugs are administered as follows with a 3-week cycle (every 21 days).

Investigational/reference product:

HLX10 or placebo, 4.5 mg/kg, once every 3 weeks (21 days)

Other study drugs: chemotherapy

- Etoposide: 100 mg/m^2, IV, on Days 1, 2, and 3 of each cycle.
- Carboplatin: AUC = 5, up to a dose of 800 mg, IV, on Day 1 of each cycle.

  Dose of carboplatin shall be calculated according to the following Calvert formula:

  - Dose of carboplatin (mg) = target AUC x [(CrCl (mL/min) + 25)]
  - Creatinine clearance (CrCl) is calculated according to the Corkroft-Gault formula (Appendix 6) on the basis of the subject's most recent serum creatinine and body weight. Note: If CrCl calculated by the Corkroft-Gault formula is > 125 mL/min, CrCl shall be calculated using an alternative formula in accordance to the standards of the study site, or capped at 125 mL/min.

A combination of HLX10 or placebo + carboplatin + etoposide shall be administered in a 3-week treatment cycle; carboplatin and etoposide are administered for a maximum of 4 cycles.

Refer to Figure 2 "Schematic of study treatment" for the regimen of each treatment arm. In each 3-week cycle, the subjects shall receive an intravenous infusion of HLX10 or placebo, followed by intravenous infusion of carboplatin + etoposide on the first day of dosing with close monitoring of vital signs. Administration of HLX10/placebo shall be blinded, while carboplatin + etoposide are openly administered. Subjects will continue to receive etoposide on Days 2 and 3. The treatment will continue until disease progression, intolerable toxicity, discontinuation decided by the subject or the investigator, death, withdrawal of informed consent, pregnancy, incompliance with protocol or

procedure requirements, administrative reasons, or other reasons specified in the protocol, whichever occurs first. The dosing window is ±3 days from the scheduled date of administration (from the date of the first dose). Drugs administered outside the dosing window is considered a delayed dose, and subsequent doses shall be administered according to the actual date of last administration. If chemotherapy is not used due to toxicity or other reasons in a certain cycle, it is not counted as the number of combined chemotherapy cycles. After completing 4 cycles of chemotherapy, even if the subject does not meet the above criteria, the chemotherapy will not be continued.

3.7.3 Dose modification

Starting from the beginning of HLX10 or placebo infusion, subjects shall be closely monitored for allergic reactions that may occur within a few minutes. In case of mild symptoms (such as flushing or local skin reactions), drugs may be administered at a slower speed. For serious hypotension, bronchospasm, or generalized rash/erythema, the administration should be stopped immediately and appropriate therapies should be given. For a life-threatening reaction, including allergic reactions, hypersensitivity reactions, renal failure, severe cardiopulmonary events, and severe skin reactions, etc., the medications shall be discontinued permanently.

The dosing window is ± 3 days from the scheduled date of administration (from the date of the first dose). Drugs administered outside the dosing window is considered a delayed dose, and subsequent doses shall be administered according to the actual date of last administration. During the course of combined treatment, if a delay of more than 2 weeks is expected due to the toxicity of chemotherapy, only HLX10 or placebo will be administered until the toxicity returns to the standard of chemotherapy administration. Chemotherapy may be continuously suspended for a maximum of 6 weeks, otherwise the chemotherapy should be discontinued. If a delay of more than 2 weeks is expected due to the toxicity of HLX10 or placebo, only chemotherapy will be administered until the toxicity recovers to the HLX10 or placebo dosing criteria. HLX10 or placebo therapy may be continuously suspended for a maximum of 12 weeks, otherwise the HLX10 or placebo will be discontinued. In case of a delay due to toxicity with equivocal association, all the study drugs shall be synchronously delayed if the event is expected to return to re-dosing standards within 2 weeks.

3.7.3.1 General principles for dose modification

Any modified or delayed doses or adopted supportive therapies should be recorded in the source documents and eCRFs. Adverse events are assessed for severity according to CTCAE v4.03.

- For concomitant conditions already present at baseline, dose modifications may be determined by the investigator based on changes in severity of toxicity. For example, if the subject already has a Grade 1 weakness at baseline, and the severity increases to Grade 2 during treatment, it may be considered to make dose modification according to Grade 1 toxicity due to 1-grade increase in toxicity.
- If multiple toxicities of different severities occur at the same time, the dose should be adjusted according to the most severe toxicity.
- If the toxicity is related to one of the study drugs only (for example, HLX10, carboplatin or etoposide) as assessed by the investigator, dose modification of that study drug only with reference to the corresponding dose modification principle is acceptable, and the subject can continue receiving the other study treatment in the absence of other contraindications.
- If the toxicity is associated with only one of the chemotherapy medications as assessed by the investigator, the dose of the other chemotherapy medication may not be adjusted.
- In the event that a delay is required for reasons of toxicity (not definitively related to which drug), similar delays of all study drugs at the same time are required if recovery to a re-dosing level is expected within 2 weeks.
- If HLX10/placebo, carboplatin, or etoposide is interrupted due to toxicity, study treatment must be restarted, keeping HLX10/placebo in sync with the chemotherapy treatment cycles.

3.7.3.2 Principles for HLX10 or placebo dose modifications

In the event of HLX10- or placebo-related toxicity, a delay in HLX10 or placebo is allowed rather than dose adjustment. Subjects who miss a scheduled infusion should be actively contacted to arrange another visit as soon as possible for administration. Administration of HLX10 or placebo may be delayed, but a dosing interval of up to 12 weeks is considered intolerable, where HLX10 or placebo will be permanently discontinued and the subject should withdraw from the trial. For a treatment delay

due to intolerance to HLX10 or placebo, chemotherapy should be administered as scheduled, and HLX10 or placebo may be postponed to the next cycle with no more than 12 weeks between doses; similarly, for a treatment delay due to intolerance to chemotherapy, chemotherapy may be postponed to the next cycle with an interval no more than 6 weeks.

3.7.3.3 Principles for chemotherapy dose modifications

In the event of intolerance to etoposide/carboplatin, doses may be adjusted twice in accordance with the prescribing information of carboplatin and etoposide and local treatment standards.

Table 1. Principles for chemotherapy dose modifications

Dose Level	Etoposide Dosing Regimen	Carboplatin Dosing Regimen
Starting Dose	100 mg/m^2, Intravenous infusion (IV) on Day 1, 2 and 3 of each 3-week (21-day) cycle.	AUC = 5, up to a dose of 800 mg, intravenous infusion (IV) on Day 1 of each 3-week (21-day) cycle.
First Dose Reduction	75% of starting dose	75% of starting dose
Second Dose Reduction	50% of starting dose	50% of starting dose

If treatment is delayed due to intolerance to chemotherapy, chemotherapy may be delayed to the next cycle of administration, with the maximum permissible interval for chemotherapy not exceeding 6 weeks.

The following are **recommended carboplatin dose modifications for hematological and non-hematological toxicities**.

Hematological toxicities

At the start of each cycle, neutrophil count (ANC) must be ≥ 1.5 × 10^9/L and platelet count (PLT) must be ≥ 100 × 10^9/L. Otherwise the treatment should be postponed for up to 42 days to provide a sufficient period for recovery. According to the guidelines of the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN), growth factors can be given to subjects with reduced ANC and/or PLT. At the beginning of subsequent cycles after recovery, dosage shall be adjusted based on the PLT and ANC nadirs of the last cycle (refer to Table 2).

Table 2. Carboplatin dose modifications for hematological toxicities

Toxicity[a]	Dose of carboplatin
ANC < 0.5 ×10^9/L and PLT ≥ 50 ×10^9/L	75% of the previous dose
PLT < 50 ×10^9/L, ANC not considered	75% of the previous dose
PLT < 50 ×10^9/L with Grade 2 hemorrhage, ANC not considered	50% of the previous dose
ANC < 1×10^9/L with fever ≥ 38.5 °C	75% of the previous dose

[a] **Nadir of the last cycle**

Doses shall be permanently reduced at the first onset of neutropenic fever or thrombocytopenia (PLT < 25 × 10^9/L or < 50 × 10^9/L with signs of bleeding or need for blood transfusion). For the need for

dose reduction at the second onset of neutropenic fever or thrombocytopenia, dose of carboplatin shall be reduced in accordance with the physician's judgement and local standard medical practices. In case of neutropenic fever or Grade 4 neutropenia, colony-stimulating factors (such as granulocyte colony-stimulating factor) may be administered in place of reduced doses in accordance with local standard medical practices and ASCO guidelines. For subjects who require a third dose reduction, the chemotherapy shall be discontinued immediately.

Subjects who require dosing modification due to both ANC and platelet count shall receive a lower dose.

Treatments may be postponed for up to 42 days until the first day when ANC is $\geq 1.5 \times 10^9$/ L and PLT is $\geq 100 \times 10^9$/L. However, if the counts fail to recover within 3 weeks, the chemotherapy shall be reduced or suspended in accordance with the physician's judgement and local standard medical practices before ANC recovery.

The investigator shall pay attention and remain alert to early and significant signs of myelosuppression, infections and neutropenic fever, to ensure a prompt and appropriate management of such complications. The investigator shall remind the subjects of the signs of such complications and encourage them to seek medical attention as soon as possible.

If chemotherapy is to be suspended due to hematological toxicities, a complete blood count (including WBC differential counts) shall be performed once a week until such counts return to the lower limit specified for the treatment. The treatment shall be completed as planned thereafter.

No dose reduction is required for anemia. Subjects shall be given supportive care in accordance with the guidelines of the institution where the attending physician is located.

Non-hematological toxicities

In the event of Grade 3 or 4 gastrointestinal toxicities, treatment shall be delayed until the measurement falls below or is equivalent to the subject's baseline value. At the beginning of the subsequent cycles, the dose shall be reduced based on the dose of the last cycle leading to gastrointestinal toxicities. The following table includes related recommendations for dosing modifications for non-hematological toxicities.

Table 3. Carboplatin dose modifications based on non-hematological toxicities in previous treatments

Toxicities		Modified carboplatin dose by % of previous dose[a]
Diarrhea	Grade 3 or 4[b]	100%
Oral mucositis	Grade 3 or 4	75%
Nausea/vomiting	Grade 3 or 4	75%

Neurotoxicity (motor or sensory)	Grade 2	100%
	Grade 3 or 4	75%
Transaminitis	Grade 3	75%
	Grade 4	Discontinuation
Others	Grade 3 or 4	75%

AUC = Area under the concentration-time curve.

[a] **Modify carboplatin dose to a specific percentage of the previous AUC, if deemed appropriate by the attending physician**

[b] **Or any severity of diarrhea that requires hospitalization.**

Nausea and/or vomiting shall be treated with an appropriate antiemetics. If Grade 3 or 4 nausea/vomiting continues despite the use of antiemetic, reduce subsequent dose by 25%. If the next dose is tolerated, restore the dose to 100% as soon as possible.

If a subject develops oral mucositis on day 1 of any cycle, suspend the treatment until the oral mucositis subsides. If oral mucositis/stomatitis does not subside within 3 weeks, discontinue carboplatin. For the subject developing Grade 3 acute oral mucositis at any time, doses are administered at 75% after the oral mucositis has completely subsided. This shall be a permanent dose reduction.

Other toxicities

If a subject experiences any Grade 3 or 4 toxicities that are not mentioned above (except alopecia), discontinue carboplatin until the subject has fully recovered or the toxicity has been relieved to Grade 1. Treatment should then be restarted at a 50% dose and this shall mark a permanent dose reduction. If the toxicity does not recover to Grade 1 within 3 weeks, carboplatin shall be discontinued. For Grade 1 and 2 toxicities, no dose reduction is needed.

Recommended etoposide dosing modifications are as follows. The investigator may adhere to the following or to his/her clinical practice during the study.

Table 4. Etoposide dose modification for subjects with renal impairment

Creatinine clearance rate (mL/min)	Dose of etoposide
>50	100%
15–50	75% of the dose

Modification of etoposide dose based on the prescribing information for etoposide and the local medical standard is permitted. Once reduced, the current dose will never return to 100%.

3.7.4 Packaging and labeling

HLX10, placebo and carboplatin-etoposide vials shall be labeled by a third party designated by the sponsor.

The label shall include: drug name, drug number, protocol number, specifications, usage and dosage, batch number, expiration date, storage requirements and other specific information required by local regulations and the Good Manufacturing Practices (GMP).

3.7.5 Storage, management, and dispensing

The study drugs shall be delivered by the sponsor or a designated third party. The study site shall establish a comprehensive procedure for study drug reception. A designee is required to receive the study drugs and sign for the receipt. Study drugs are only used in trials specified in this study protocol. Only authorized personnel may have access to these drugs.

The study site shall establish a strict and designated drug management system for the storage and dispensing of study drugs, as well as a registration system. The site should ensure that the storage conditions of the study drugs are in compliance with the regulations, and shall document such conditions and keep the records.

Only the investigator or assigned personnel may administer the medications to the subject and manage such medications. The dispensing and retrieval of every dose shall be documented on a specified log in a timely manner. Any loss, missing or misuse of study drugs shall be documented in detail.

The retrieval and disposition of study drugs shall be undertaken by the sponsor or its designated third party to prevent the drugs from entering the market.

For details, please refer to the drug management and operating procedure.

3.7.6 Concomitant medication

The investigator may, at his/her discretion, administer any drugs that he/she deems necessary for the treatment of subjects and are not expected to interfere with the evaluation of the study drugs (i.e., the best supportive care). Prophylactic and other supportive treatment for nausea and vomiting may be given to subjects according to local medical practice before and after carboplatin and etoposide administration.

All concomitant medications (including start/end dates, total daily doses, and indications) must be documented in the subject's source document and in the corresponding section in the electronic case report form (eCRF).

Prohibited medications/therapies

Medications and therapies which are prohibited during the study include:

- Any other therapy with anti-tumor effects, including systemic chemotherapy, radiotherapy, immunotherapy, biotherapy, molecular targeted therapy, or NMPA-approved anti-tumor modern Chinese medical formulations for marketing (refer to Appendix 9), immunomodulating adjuvants with anti-tumor effects (such as thymosin, lentinan, interleukin-12), etc.; localized treatment of isolated lesions (other than the target lesion) may be accepted (e.g., local surgery or radiotherapy for bone metastases);
- Any other clinical investigational drugs;
- Immunosuppressants include, but are not limited to, prednisone of over 10 mg/day, or equivalent systemic corticosteroids, methotrexate, azathioprine, and TNF-α blockers, with the exceptions of:
  - ✓ management of study treatment-related AEs with immunosuppressants;
  - ✓ short-term prophylactic use in a subject who is scheduled to receive chemotherapy, when the prescribing information requests for corticosteroids to be administered to patients with known hypersensitivity;
  - ✓ use in subjects who are allergic to contrast agents;
  - ✓ use of inhaled, topical and intranasal corticosteroids;
  - ✓ short-term use of corticosteroids when clinical indications are present and when deemed necessary by the investigator for disease management (e.g., for chronic obstructive pulmonary disease, radiation therapy, nausea, etc.).
- Live vaccines within 4 weeks prior to the first study dose and throughout the trial, including but not limited to: measles, mumps, rubella, chickenpox, yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid vaccines. Subjects may receive live attenuated influenza vaccines for seasonal flu, provided that they are not administered via the intranasal route.

Permitted medications/therapies

Medications and therapies which are permitted during the study include:

- Treatment for complications, adverse events or symptoms (including blood products, blood transfusions, infusions, antibiotics, anti-diarrheal medications, etc.), with the exception of medications/therapies which are expected to interfere (or interact) with the evaluation of the study;

- Antiemetics;
- Nutritional support;
- Medication or therapy necessary for previous disease.

3.7.7 Medication compliance

During the study and follow-up periods, details of study medications shall be recorded in the eCRF. Any deviations from the protocol shall be recorded in the eCRF, including the date of and reason for such deviations. The Clinical Research Associate (CRA) shall review the medication compliance during visits to the study site and at the end of the study.

4 STUDY PROCEDURES AND VISITS

For an overview of the study procedures, see the study events flow chart. All study results will be recorded in eCRF. Each scheduled visit must be completed within the specified time window (see study flow chart).

4.1 Study Procedures

4.1.1 Demographics and medical history

Demographics contain information on date of birth, gender, ethnicity, etc.

At screening, lung cancer history of subjects must be collected, including: clinical phase, pathological diagnosis, diagnosis method, diagnosis date and prior medications (surgical history, radiotherapy/chemotherapy history, etc.). Subjects' personal histories are also collected, including allergy history, drug dependence history, smoking and drinking; in addition, histories of other important diseases within one year prior to signing the informed consent form must be collected.

4.1.2 Prior and concomitant medications

All prior and concomitant medications are recorded from 30 days prior to signing the informed consent through the safety follow-up visit should be recorded. Concomitant medications associated with AEs are recorded up to 90 days after the last study treatment. Prior and concomitant medications (including

traditional Chinese medicine) are collected and recorded in the eCRF.

4.1.3 Adverse Events

All AEs and treatment emergent AEs are recorded from the time of signing the ICF until 90 days after the last study treatment. If a subject started a new antineoplastic therapy during the AE collection period, only information on AEs related to study treatment are collected after the new antineoplastic therapy.

4.1.4 Quality of life assessment

In this study, subjects will be assessed for quality of life, including by EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-LC13.

4.1.4.1 EQ-5D-5L

The EQ-5D is a standardized measure of health status developed by the EuroQol group that allows a simple and general rating of health status from a clinical and economic evaluation perspective (EuroQol Group 1990). The scale is applicable to a variety of health conditions and treatments. It lists simple descriptive features, gives single index values for health state, and can be used for clinical and economic evaluation of health treatments as well as population health surveys. This questionnaire contains 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect an increased degree of severity (EuroQol Group, 2013). Since 2009, the EuroQol group has developed a more sensitive EQ-5D version (EQ-5D-5L) in which the range of responses for each dimension is expanded, i.e., from three levels of increasing severity to five (Herdman et al, 2011). Preliminary studies have shown that, compared to the nature of the 3-level version of the measured parameters, the 5-level version improved in the following aspects: reduced ceiling effects, increased robustness, and enhanced ability to distinguish between different health levels.

During the study, subjects are asked to select the most appropriate level from the five dimensions described above, indicating their current health status. The questionnaire also includes a visual analog

scale in which subjects will be asked to rate their current health state on a scale from 0 to 100, with 0 indicating the worst health state (see Appendix 3).

4.1.4.2 EORTC QLQ-C30

The EORTC QLQ-C30 v3 questionnaire is an established measure of health-related quality of life (HRQoL) and is commonly used as an endpoint in oncology clinical trials. The questionnaire assesses HRQoL/health status through 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, nausea and vomiting), and 1 global health and QoL (quality of life) scale. The 6 individual symptom measures include: dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties (see Appendix 3). For the 15 domains described above, the total score is standardized to a range from 0 to 100, where higher scores indicate stronger functioning, higher HRQoL or higher symptom levels.

4.1.4.3 EORTC QLQ-LC13

The QLQ-LC13 is a 13-item self-administered questionnaire for lung cancer disease that will be used along with the EORTC QLQ-C30. The scale includes both multiple and single lung cancer-related symptom parameters (i.e., cough, hemoptysis, dyspnea and pain), as well as side effects of conventional chemotherapy and radiotherapy (i.e., alopecia, neurological disorders, oral pain and dysphagia). Similar to the EORTC QLQ-C30, all questions (except one) are on a 4-point scale: "not at all", "a little", "quite a bit", and "very much". Only 1 question (43rd question "Did you take any medicine for pain?") is with response options of "yes" or "no". The QLQ-LC13 are scored similarly to the EORTC QLQ-C30.

4.1.5 Echocardiography

Echocardiography must be performed for all subjects at screening, and the results of left ventricular ejection fraction are recorded.

During the study treatment, if the subject has clinical symptoms such as shortness of breath, tachycardia, cough, jugular vein distention and hepatomegaly, relevant examinations must be timely performed after assessed by the investigator.

4.1.6 12-lead ECG;

Subjects will rest for 5 minutes before each 12-lead ECG. In case of clinically significant ECG abnormalities at a visit, a re-examination is recommended within 24 hours.

4.1.7 Complete physical examination

At screening, the subjects shall have a complete physical examination including head and neck (including thyroid gland), chest (including heart and lung), abdomen (liver, gallbladder, spleen and kidney), limbs, skin, lymph nodes, nervous system as well as the general conditions of subjects, with the examination results recorded; special attention should be paid to the symptoms and signs in respiratory system.

4.1.8 Symptom-directed physical examination

A symptom-directed physical examination will be performed by the investigator during study treatment based on clinical observations and symptoms. Clinically significant physical examination abnormalities that are judged by the investigator to be significantly worse than the screening period or newly developed should be recorded as adverse events.

4.1.9 Height, weight and vital signs

Height is measured only at screening.

Vital signs should be assessed after the subject has rested for at least 5 minutes, including blood pressure (mmHg), pulse (beats/min), respiratory rate (breaths/min) and body temperature (°C), and body weight should be recorded.

Body weight and vital signs are to be measured prior to each dose during study treatment. No dose adjustment of the study drug is required if the subject's body weight differs ≤ 10% from the reference value of the current dose, otherwise the dose should be recalculated.

4.1.10 ECOG scores

Evaluation of ECOG performance status by the investigator is recommended throughout the study. The first ECOG score should be completed within 7 days prior to randomization.

4.1.11 Local laboratory tests

Local laboratory tests performed at study sites include routine blood test, biochemistry, coagulation, urinalysis, thyroid function, virology and pregnancy test. Routine blood test, biochemistry, coagulation and urinalysis should be performed within 3 days pre-dose in each treatment cycle; for combined chemotherapy, routine blood tests should be performed on Day 8 (± 3 days) of each treatment cycle to closely monitor bone marrow suppression. For aforementioned laboratory tests scheduled on the same day as study treatment, the study treatment can be arranged only after the test results are obtained. During the treatment period, thyroid function and blood pregnancy (for females of childbearing age only) tests are performed 3 days pre-dose every 2 cycles

Table 5. Local laboratory tests

Routine blood test	Biochemistry	Urinalysis[b]	Others
Red blood cells Haemoglobin Platelet White blood cells WBC differential counts and percentages • Basophils • Eosinophils • Lymphocyte • Monocytes • Neutrophils	Urea/urea nitrogen Creatinine Bicarbonate[a] Blood glucose Total bilirubin Direct bilirubin ALT AST ALP Lactate dehydrogenase Total cholesterol Total protein Albumin Sodium Potassium Magnesium Chlorine Calcium	Urine specific gravity Urine pH Urine protein Urine glucose Urine ketones Urine occult blood Urine white blood cells In case of abnormalities, microscopically examine: white blood cells red blood cells	**Coagulation function** International normalized ratio (INR) Activated partial prothrombin time (APTT) **Thyroid function tests** Triiodothyronine (T3 or FT3) Thyroxine (T4 or FT4) Thyroid stimulating hormone (TSH) **Virology[C]** Hepatitis B surface antigen (HBsAg) HBs antibody (HBsAb) Hepatitis B E-antigen (HBeAg) HBe antibody (HBeAb) HBc antibody (HBcAb) Hepatitis C virus (HCV)

	Phosphorus		antibody HBV-DNA (optional) HCV-RNA (optional) Anti-HIV
			Pregnancy test[d]

a. Bicarbonate/carbon dioxide binding capacity/total carbon dioxide (TCO_2)
b. If a subject has two consecutive 2++ urine protein or one ≥ 3+++, urine protein should be tested at 24 hours;
c. All subjects are tested for HBsAg or HCV antibody at screening; HBsAg positive subjects should be further tested for HBV DNA titer; and HCV antibody positive subjects should be further tested for HCV RNA. In case of HBV DNA (-) and: 1) HBsAg (+), or 2) HBcAb (+) and HBsAg (-) at baseline, HBV antibody and HBV DNA should be tested every 2 cycles during the treatment period. In case of HCV antibody (+) and HCV RNA (-) at baseline, HCV antibody and HCV RNA should be tested every 2 cycles during the treatment period.
d. Women of childbearing potential should have a blood pregnancy test within 7 days prior to randomization and must have a negative result for enrollment; this is also tested within 3 days pre-dose every 2 cycles.

4.1.12 Central laboratory assessments

PK and ADA samples of HLX10 or placebo are collected and sent to the central laboratory for evaluation. PK and ADA samples for HLX10 or placebo will be collected at the following time points: Within 7 days pre-dose in Cycle 1, within 3 days pre-dose in Cycles 2, 4, 6, 8 and every 4 cycles thereafter, within 2 hours after the end of dosing in Cycles 1 and 8 of treatment period (for PK only), and at EOT visit and safety follow-up.

Table 6. PK and ADA blood sampling

Study visits		Blood sampling	PK[a]	ADA[b]
Treatment period	Cycle 1	Within 7 days pre-dose	X	X
		Within 2 hours post-dose	X	-
	Cycle 2	Within 3 days pre-dose	X	X
	Cycle 4	Within 3 days pre-dose	X	X
	Cycle 6	Within 3 days pre-dose	X	X
	Cycle 8	Within 3 days pre-dose	X	X
		Within 2 hours post-dose	X	-
	Every 4 cycles thereafter	Within 3 days pre-dose	X	X
Discontinuation		-	X	X
Safety follow-up		-	X	X

a. Blood samples for HLX10 PK are collected within 2 hours after the end of HLX10 or placebo administration in Cycles 1 and 8 of the treatment period.

b. **ADA samples will only be collected pre-dose** and procedures are described in the laboratory manual.

4.1.13 Tumor imaging

Imaging studies in this trial include computed tomography or magnetic resonance imaging (CT/MRI). Images will be assessed by the IRRC according to RECIST v1.1 (see Appendix 2-1) and modified RECIST criteria (see Appendix 2-2). The parameters (such as slice thickness and field of view) used for all follow-up imaging should be consistent with those at baseline. CT/MRI scans must meet the criteria for imaging lesions in the corresponding organ system.

Subjects should undergo CT or MRI (including brain, chest, abdomen, pelvic cavity and any other sites suspected of having tumor lesions) at screening (within 4 weeks pre-dose), every 6 weeks (± 7 days) during the first 48 weeks after the start of study treatment, and every 9 weeks (± 7 days) after week 48. Wherein,

At **screening**, bone scans are required for all subjects. Positive scans should be confirmed by CT/MRI, and re-examinations are determined by the investigator according to clinical needs during the treatment

period. Brain MRI is also required at screening, but for subjects with contraindication, brain CTs are acceptable. The investigator and IRRC respectively assess the tumor images according to RECIST v1.1 (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation. If tumor assessment has been performed within 28 days prior to the first dose by the same methods and devices in the same hospital, it may serve as the baseline tumor assessment.

Tumor imaging studies are conducted every 6 weeks (± 7 days) for the first 48 weeks **after the start of study treatment** and every 9 weeks (± 7 days) after week 48, regardless of dose delay.

At the EOT visit, if tumor imaging has been performed within the last 4 weeks, a re-test is not required.

For subjects who discontinued for reasons other than disease progression, imaging assessments are to be continued as scheduled (at the same frequency as if the subject have remained on study treatment , i.e., every 6 weeks (± 7 days) for the first 48 weeks and every 9 weeks (± 7 days) after 48 weeks), until disease progression, initiation of new antineoplastic therapy, withdrawal of ICF, death, or end of study, whichever occurs first.

4.1.14 Biomarker sample collection

At screening, blood samples must be collected for biomarkers detecting. To the extent possible, formalin-fixed paraffin-embedded (FFPE) tumor samples (paraffin blocks or 10 unstained 3–4 μm sections) collected at or after the diagnosis of ES-SCLC and within 6 months prior to the start of study medication or pathological reports of such specimens should also be provided. In case of no archived tumor tissue samples available, it is recommended to conduct a fresh tumor lesion biopsy at screening to obtain the corresponding tumor sample (the number of specimens required is based on the biopsy result). Tumor tissue sections will be used for immunohistochemical analysis to evaluate the expression level of PD-L1 in tumor cells and tumor-infiltrating immune cells. Freshly collected specimens, radical resections, core needle biopsy, excisions, incisions, punch or clamp biopsies are acceptable. Fine-needle aspirations (i.e., samples that lack a complete tissue structure and provide only cell suspension and/or cell smear), brush biopsies, cell pellet samples from pleural effusions and bronchoalveolar lavage fluid samples are unacceptable. For detailed requirements for tissue samples, see the laboratory manual.

4.2 Screening Period (Day -28 to -1)

The Informed Consent Form (ICF) must be signed and dated by the subject or legal representative prior to conducting study-related procedures.

The screening period should not exceed 28 days, beginning from the subject signing and dating the informed consent form and ending when the subject is randomized or fails screening. In this study, one re-screening is allowed for ineligible subjects: in case of unqualified laboratory tests, one re-test can be performed within the screening time window, without giving a new screening number; for other conditions incompliant with the inclusion/exclusion criteria, subjects should be re-screened with a new screening number.

Subjects must complete the following study procedures or assessments at screening:

1) Signing informed consent form
2) Demographics and medical history
3) Prior and concomitant medications
4) Adverse events
5) Quality of life assessment (Day -7 to -1)
6) Echocardiography
7) 12-lead ECG;
8) Complete physical examination
9) Height, weight and vital signs
10) ECOG scores (Day -7 to -1)
11) Local laboratory tests: routine blood test, biochemistry, coagulation, urinalysis, thyroid function, pregnancy test (for females of childbearing age only) and virology. Tests other than virology should be completed within 7 days before randomization.
12) Tumor imaging:

    CT or MRI should be performed at screening (on sites including brain, chest, abdomen, pelvic cavity and any other sites suspected to have tumor lesions). At screening, bone scans are required for all subjects. Positive scans should be confirmed by CT/MRI. Brain MRI is also required at screening, but for subjects with contraindication, brain CTs are acceptable. If tumor assessment has been performed within 28 days prior to the first dose by the same methods and devices in

the same hospital, it may serve as the baseline tumor assessment.

13) Biomarker sample collection: Tumor tissue and blood samples are collected for biomarker detection.

4.3 Treatment period

The treatment period begins with the subject's enrollment, and the first dose should be administered within 3 days after randomization. Study drugs are given every 3 weeks until disease progression, intolerable toxicity, discontinuation decided by the subject or the investigator, death, withdrawal of informed consent, pregnancy, incompliance with protocol or procedure requirements, administrative reasons, or other reasons specified in the protocol, whichever occurs first. See Figure 2 "Schematic of study treatment" for details.

Subjects will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each subject. Also, subjects are assessed for toxicity prior to each dose; doses are only given when clinical assessments and local laboratory tests are acceptable.

Treatment should be discontinued when they have evidence of disease progression as assessed by RECIST v1.1. However, considering the limited availability and efficacy or greater toxicity of treatment options after withdrawal, and for better adaptation to standard clinical practice, the subject who **meets all the following conditions** may continue the treatment as determined by the investigator and after appropriate discussion with the subject and obtaining the informed consent.

(1) With no clinical signs and symptoms (including worsening of laboratory findings) indicating a significant disease progression.

(2) A stable Eastern Cooperative Oncology Group (ECOG) performance status score.

(3) No rapid disease progression or tumor progression requiring urgent alternative medical intervention at critical anatomical sites (e.g., spinal cord compression).

(4) The major organ function meets the inclusion and exclusion criteria of this study.

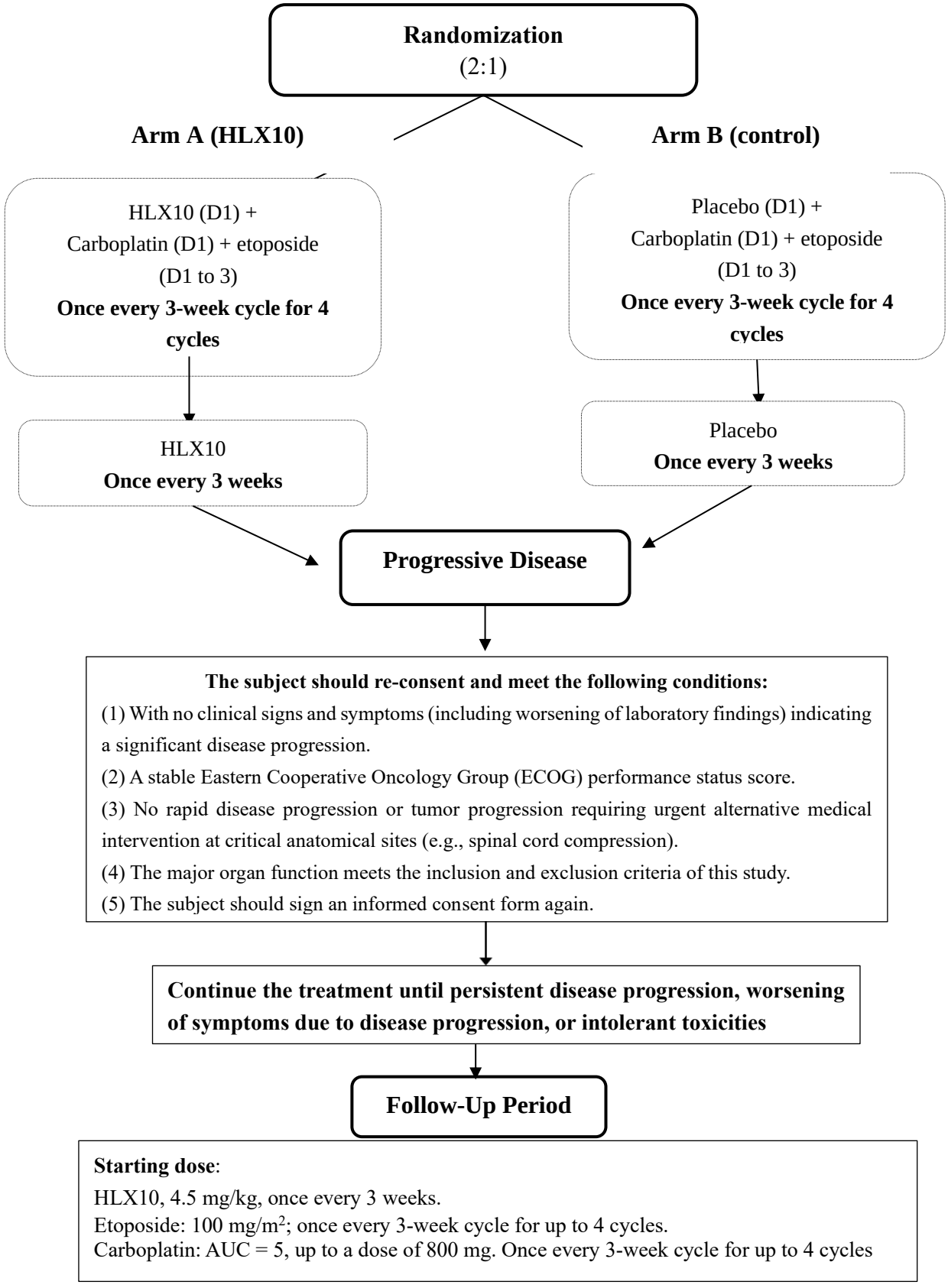
(5) The subject should sign an informed consent form again.

Such subjects should be closely monitored with imaging assessments within 6 weeks or as soon as possible if symptoms worsen. Treatment should be discontinued at any time if clinical worsening due to disease progression is noted or if continuous disease progression is confirmed by subsequent

imaging assessments. In addition, treatment is to be discontinued if, in the judgment of investigator, the subject experiences intolerable toxicities or worsening of symptoms or has other evidence of disease progression based on imaging assessments and a global assessment of clinical condition.

Subjects who re-consent after disease progression should complete the screening assessment for continuation of treatment within 28 days after confirmation of disease progression (in case of a need for recovery due to AEs, a maximum of 42 days from the end of previous study treatment is allowed). The imaging test confirming the subject's disease progression (first PD) can serve as the baseline for further treatment if the following two conditions are met: (1) an interval of no more than 28 days from the imaging test to the start of further treatment; (2) no study treatment has been done after that imaging test; otherwise the baseline imaging assessments should be performed again before further treatment. The study treatment visit will be continued every 3 weeks after the start of further treatment, and the visits will be scheduled as those in the treatment period.

Figure 2. Schematic of study treatment



The following study procedures must be completed at each visit during treatment period:

1) Concomitant medications;

2) Adverse events
3) Quality of life assessment: prior to the first dose and every other subsequent dosing cycle (i.e., pre-dose in Cycles 1, 3, 5, 7, etc.) until EOT. Re-assessments are not required for subjects who had a quality of life assessment on Day -7 to Day -1 of the screening period.
4) 12-lead ECG;
5) Symptom-directed physical examination;
6) Weight and vital signs;
7) ECOG scores
8) Survival status;
9) Local laboratory tests: routine blood test, biochemistry, coagulation, urinalysis, thyroid function, pregnancy test (for females of childbearing age only) and virology (if necessary);
   - Routine blood test, biochemistry, coagulation and urinalysis should be performed within 3 days pre-dose in each treatment cycle; for combined chemotherapy, routine blood tests should be performed on Day 8 (± 3 days) of each treatment cycle.
   - Thyroid function must be tested at the local site within 3 days pre-dose every 2 cycles.
   - Serum pregnancy test must be performed for women of childbearing age at the local site within 3 days pre-dose every 2 cycles during the treatment period.
   - In case of HBV DNA (-) and: 1) HBsAg (+), or 2) HBcAb (+) and HBsAg (-) at baseline, HBV antibody and HBV DNA should be tested every 2 cycles during the treatment period. In case ofHCV antibody (+) and HCV RNA (-) at baseline, HCV antibody and HCV RNA should be tested every 2 cycles during the treatment period.

   For aforementioned laboratory tests scheduled on the same day as study treatment, the study treatment can be arranged only after the test results are obtained
10) Central laboratory assessments: including HLX10 or placebo-PK, HLX10 or placebo-ADA sample collections
11) Study treatment

Study drugs, including HLX10/placebo, carboplatin and etoposide, are administered on Day 1 of each cycle after all clinical and laboratory operations/assessments are completed.

12) Tumor imaging assessments

CT or MRI should be performed every 6 weeks (± 7 days) during the first 48 weeks after the start

of study treatment, and every 9 weeks (± 7 days) after week 48 on sites including brain, chest, abdomen, pelvic cavity and any other sites suspected to have tumor lesions; examination methods at the same site should be consistent as much as possible throughout the study; if there are no contraindications, contrast agent should be used. The investigator and IRRC should assess the tumor images according to RECIST v1.1 (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation.

4.4 End-of-Treatment Visit

For any subject withdrawing from the study or terminating the study regardless of causality, a end-of-treatment (EOT) visit should be performed, where possible, in 7 days after the end of treatment is learned of or confirmed (and should be done prior to initiation of any new anti-tumor treatment in the subject). During the visit, the investigator shall collect the following information.

1) Concomitant therapy
2) Adverse events
3) Quality-of-life assessment: One quality-of-life assessment should be performed at this visit if such assessment has never been done in the past 3 weeks.
4) 12-lead ECG
5) Symptom-oriented physical examination
6) Body weight and vital signs
7) ECOG score
8) Survival status
9) Local laboratory tests: including routine blood test, blood chemistry test, coagulation test, routine urine test, thyroid function test, pregnancy test (in women of child-bearing age only), and virological test (when necessary);
   - Retest may be waived if it is not more than 3 weeks from the last thyroid function test.
   - If, 1. HBV DNA(-) and HBsAg(+) or 2. HBcAb(+) and HBsAg(-) during screening period (baseline), and it is more than 3 weeks from the last test, then HBV antibody assay and HBV DNA assay should be performed at the study termination visit. If HCV antibody(+)

and HCV RNA(-) at baseline, and it is more than 3 weeks from the last test, then HCV antibody assay and HCV RNA assay should be performed at the study termination visit.

10) Central laboratory assessment: including HLX10 or placebo-PK blood sampling and HLX10 or placebo-ADA blood sampling
11) Radiologic tumor assessment: If any radiologic tumor assessment has been done in the first 4 weeks, then it may be unnecessary to repeat radiologic tumor assessment at the termination visit.

4.5 Follow-Up Period

After the EOT visit, subjects will be followed up. If a subject terminates the study not because of progressive disease (PD), then radiologic assessment should be further performed according to an established schedule, where possible, until PD, initiation of a new anti-tumor therapy, ICF withdrawal, death or study completion (whichever occurs first).

4.5.1 Safety follow-up period

Subjects should be subjected to safety follow-up in 90 days after the final dose, and AEs in subjects will be collected. Each subject shall come to the study center for safety follow-up 30 (±7) days after the final dose; if the EOT visit is delayed regardless of causality 30 (±7) days after the final study treatment, then the safety follow-up visit will no longer be performed. One safety follow-up should be performed by phone 90 (±7) days after the final dose in each subject, in which information of the subject about AEs and AE-related concomitant therapy only will be collected. If the patient starts a new anti-tumor therapy during AE collection period, only AE information related to the study treatment need be collected after the initiation of the new anti-tumor therapy. Safety information should be acquired by phone with a window period of ±7 days. Safety follow-up assessment 30 (±7) days after the final dose includes:

1) Concomitant therapy
2) Adverse events
3) Quality-of-life assessment
4) 12-lead ECG

5) Symptom-oriented physical examination
6) Body weight and vital signs
7) ECOG score
8) Documenting subsequent anti-tumor therapies
9) Documenting survival status
10) Local laboratory tests: including routine blood test, blood chemistry test, coagulation test, routine urine test, thyroid function test, pregnancy test (in females of child-bearing age only), and virological test (when necessary);
    - Retest may be waived if it is not more than 3 weeks from the last thyroid function test.
    - If, 1. HBV DNA(-) and HBsAg(+) or 2. HBcAb(+) and HBsAg(-) during screening period (baseline), and it is more than 3 weeks from the last test, then HBV antibody assay and HBV DNA assay should be performed at the safety follow-up visit. If HCV antibody(+) and HCV RNA(-)at baseline, and it is more than 3 weeks from the last test, then HCV antibody assay and HCV RNA assay should be performed at the safety visit.
11) Central laboratory assessment: including HLX10 or placebo-PK blood sampling and HLX10 or placebo-ADA blood sampling

4.5.2 Survival follow-up

During the survival follow-up period, subjects without PD and not receiving any other anti-tumor therapy should return to the hospital according to the established schedule for radiologic assessment follow-up, until PD, initiation of a new anti-tumor therapy, ICF withdrawal, death or study completion (whichever occurs first); while subjects experiencing PD or undergoing any other anti-tumor therapy just need to be followed up for survival status by telephone call (TC) once every 12 weeks (±7 days).

The following assessments shall be done at each follow-up visit:

1) Documenting survival status.
2) Documenting subsequent anti-tumor therapies.

4.6 Study Assessments

4.6.1 Efficacy assessment

Except overall survival, other efficacy endpoints are evaluated based on tumor response as per RECIST 1.1. Tumor assessment will be performed by qualified personnel in each study center and independent radiologic review committee (IRRC). Therapeutic decision will be made based on tumor response assessment verified by the investigator. These results will be reported in eCRF.

Tumor assessment schedule is not influenced by treatment interruption or any other event leading to imbalance in disease assessment time between treatment groups.

Progression-free survival (PFS) is defined as a period from randomization initiation through the first objective PD or death (on account of any cause without PD). PFS will be always obtained based on scan/assessment date instead of visit date.

Overall survival (OS) is defined as a period from randomization through death regardless of causality.

Objective response rate (ORR) is defined as the percentage of subjects whose best overall responses are evaluated as CR or PR.

Duration of response (DOR) is defined as a period from the first documentation of response (CR or PR) through the first documentation of PD or death (whichever occurs first). Response termination date should be consistent with the date of PD or death regardless of causality for evaluation of PFS endpoint as per RECIST 1.1.

4.6.2 Safety assessment

Safety assessment consists of monitoring and documenting all adverse events (including serious adverse events), laboratory tests (routine blood test, blood chemistry test, coagulation test, routine urine test, and thyroid function test), 12-lead ECG, vital signs, and physical examination.

4.7 Adverse Events

4.7.1 Definition of AE

Adverse event (AE) is defined as any adverse medical event occurring in a subject after receiving a

drug in a clinical trial, not definitely having causality to treatment. Therefore, an AE can be any clinically significant manifestation (e.g., a clinically significant outlier in laboratory findings), symptom or disease, regardless of relevance to the study drug.

In the event of any outlier, it should be determined according to the following criteria whether the objective outlier should be reported as an AE or not:

- The finding is associated with a symptom, and (or)
- The finding necessitates further diagnostic examination or drug/surgery intervention, and (or)
- The finding leads to dose adjustment (out-of-protocol-specification dose adjustment) or
- The finding constitutes an AE in the opinion of the investigator or the sponsor.

If none of the above criteria is satisfied, then repeated outliers alone will not constitute an AE. It is unnecessary to report any incorrectly reported finding as an AE.

Any concomitant disease, which is manifested upon signing Informed Consent Form and does not worsen in either severity or onset frequency during the study, is defined as a baseline medical condition, rather than an AE/SAE. However, if such concomitant disease in a subject is exacerbated, resulting in any complication or increased onset frequency, then such exacerbation or complication should be documented as an AE correspondingly. The investigator shall ensure that any documented event term is able to reflect the change of this condition (e.g., “exacerbation of ...”).

4.7.1.1 Progressive disease

Progression of any underlying disease, i.e., underlying tumor, should not be reported as an AE, and if its explicit manifestation is consistent with suspected progression of the underlying tumor defined in RECIST v1.1 and a subject is admitted just because of progression of the underlying tumor, then this PD should not be reported as an SAE. If it cannot be verified that a symptom is completely due to progression of underlying tumor, or a symptom does not conform to expected manifestation of PD in this study, then the progressing clinical symptom can be reported as an AE. If it cannot be verified that an AE is caused by underlying tumor only, then this AE should be reported as an AE/SAE.

4.7.1.2 New tumor

Onset of any new tumor should be regarded as an SAE. New primary tumor refers to a cancer that is

not a dominant cause of study drug treatment and is discovered after subject enrollment.

4.7.1.3 Death

All deaths occurring during the study or during follow-up period following the final dose of the study drug as specified in the study protocol have to be reported according to the following requirements:

- Any death confirmed to be PD-induced should be reported to the sponsor at the next monitoring visit. It should be documented but not reported as an SAE.
- When a death is not (or not explicitly) due to PD, the AE resulting in this death has to be deemed as an SAE and reported to the clinical research associate (CRA), the sponsor, or a representative of the sponsor in 24 h. The report should include comments regarding whether the death is concurrently complicated by PD or not (if applicable), and provide main cause of the death.
- Any death from unknown cause should be reported as an SAE with the comment "death from unknown cause". The cause of death should be further explained during follow-up. An autopsy may help assess the cause of death. If an autopsy is performed, the autopsy report should be submitted to the sponsor's pharmacovigilance team or its representative as soon as possible.

4.7.1.4 Overdose

Drug overdose means that a subject receive (intentionally or accidentally) a drug dose in excess of the dose specified in the protocol. In the event of drug overdose, appropriate symptomatic and supportive therapies may be performed in the subject. Any overdose-induced adverse reaction should be reported to CRA and included in a standard AE report.

Any drug overdose complicated by SAE will be reported in the form and the time frame pursuant to the standard SAE report.

4.7.1.5 Immune-related adverse event (irAE)

Immune-related adverse event (irAE) refers to an AE that is related to drug exposure and in conformity with immune-mediated mechanism of action without any other definitive pathological factor.

Serological, immunological and histological (biopsy) data should be used to support diagnosis of irAE when appropriate. Appropriate methods should be used to exclude pathological factors of irAE such as tumor, infection, metabolism, toxin, etc. More detailed guidance on its assessment and treatment is described in Appendix 8.

For any suspected irAE, related system functions need to be closely observed and adequate assessment shall be carried out to identify etiology and exclude other potential causes. In general, depending on severity of an AE, HLX10 (or placebo) should be suspended or permanently terminated, and/or symptomatic treatment (e.g., glucocorticoids) may be given. If the AE is not improved or is worsened after glucocorticoid therapy, one can consider increasing the dose of glucocorticoid and/or using any other systemic immunosuppressant. When grade of an AE is <1, dose of glucocorticoid can be reduced gradually and the treatment has to persist for at least 1 month. When an AE is recovered to < grade 1 and dose of glucocorticoid is reduced to prednisone (or another drug with equal potency) with a daily dose <10 mg, HLX10 or placebo transfusion may continue. In the event of recurrence of any grade 3 or above irAE (except for endocrine system disorders), permanent discontinuation and study withdrawal have to be done immediately.

4.7.2 Definition of SAE

Serious adverse event (SAE): AEs occurring during a clinical trial in conformity with any or more of the following circumstances should be deemed as SAEs:

1) Leading to death
2) Life-threatening (AE occurrence leads to an immediate risk of subject death, not including those AEs that may lead to death after PD, e.g., drug-induced hepatitis without liver failure)
3) Necessitating hospitalization or prolonged length of stay; if a subject develops a discomfort or disease prior to study enrollment and is planned to be admitted for treatment and/or surgery before or during the study but does not present with exacerbation in an unexpected manner during the study, then this event will not be classified as an SAE
4) Leading to permanent or serious disability/insufficiency
5) Leading to congenital malformation/birth defect
6) Other significant medical events: Based on scientific medical judgment, it has to be decided

whether reporting is to be expedited or not, and if the significant medical event might not immediately threaten the life, lead to death or hospitalization but some medical measures have to be taken to prevent any of the aforesaid circumstances from occurring, then this event will be normally deemed serious. For example, important treatment in A&E or domestic anaphylactic bronchospasm, non-nosocomial cachexia or convulsion, drug dependence or addiction, etc.

Note: Hospitalization or prolonged hospitalization on account of any non-AE cause/convenience (for purpose of health insurance reimbursement, etc.) or simply for clinical trial purpose does not meet the criteria for medical event and thus should not be considered as an SAE. However, each event leading to unexpected hospitalization or prolonged selective length of stay (e.g., any unexpected results of drug treatment) has to be documented and reported as an AE/SAE.

Hospitalization also includes nosocomial transfers to emergency/ICU ward (such as transfer from pediatrics to internal medicine, transfer from internal medicine to ICU ward for patients with coronary heart disease, transfer from neurology to TB ward, etc.).

Hospitalization in the following institutions are excluded:

- Rehabilitation facilities;
- Hospice care centers;
- Short-term care facilities (e.g., care provided by nursing assistants);
- Specialized nursing facilities;
- Nursing home;
- Routine observation in A&E department;
- Day surgery (outpatient treatment/diurnal surgery/diurnal operation).

Hospitalization or prolonged hospitalization due to any of the following causes is not classified as an SAE:

- Hospitalization for treatment of any original disease unrelated to any new AE or worsening of any original adverse disease (for example, inspection of persistent laboratory outliers existing prior to treatment);
- Hospitalization due to any non-medical cause (e.g., homelessness);
- Transactional hospitalization (e.g., routine checkup);
- Hospitalization specified in the study protocol (e.g., operation required for implementation of the study protocol);

- Voluntary hospitalization that will not give rise to any clinical AE (e.g., for elective plastic surgery);
- Treatment or surgery planned in the study protocol and (or) for individual subjects should be documented in baseline documents;
- Hospitalization specifically for use of the study drug.

Diagnostic and therapeutic non-invasive/invasive operations, such as surgeries, should not be reported as AEs. Nonetheless, if diseases that such operations are intended to treat meet the definition of AE, then such operations should be reported as AEs. For example, acute appendicitis occurring during AE reporting should be reported as an AE, and appendectomy for treating the disease should be documented as treatment for this AE.

4.7.3 Documentation of AEs

All AEs occurring in a period from signing Informed Consent Form through 90 days after the final administration of the study drug (including chemotherapy drugs) should be documented in corresponding AE pages in EDC. The investigator shall provide all detailed information required to be completed, including date of onset, severity, action, outcome, and causality to the study drug. When collecting AE data, one has better recording diagnosis information (if possible), rather than recording a number of signs and symptoms. However, if a diagnosis is known but the patient still has other symptoms or signs not contributing to such diagnosis, then each symptom or sign should be documented separately.

All AEs/SAEs occurring in a period from signing Informed Consent Form through 90 days after the final dose of the study drug should be documented, and the following information has to be collected:

- AE
- Onset date and end date of the AE
- CTCAE grade
- SAE or not
- Causality between the AE and the study drug as assessed by the investigator
- Actions against the study drug
- Therapeutic actions against the AE

- Outcome
- irAE or not
- In addition, the following information will be collected for each SAE:
- Date when the AE meets SAE criteria
- Date when the investigator learns of the SAE
- Justification of SAE
- Date of discharge (if applicable)
- Potential cause of death (if applicable)
- Date of death (if applicable)
- Autopsy findings (if applicable)
- Assessment of causality between the AE and study operation
- Assessment of causality between the AE and other drugs
- Description of the AE

Note: If the investigator learns, after a subject has completed safety follow-up or withdrawn from the study, that the subject experienced any SAE (including death) and reasonably considers that this event is possibly related to the study drug, then the investigator should report it to the sponsor's pharmacovigilance team or representative.

4.7.3.1 Severity of AEs

National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) V4.03 is used to document severity of AEs, classified in grades 1–5.

Grade	CTCAE Description
1	Mild: No or mild symptom; only clinical or diagnostic observation is required; action is not needed.
2	Moderate: Small-scope, local or non-invasive action is needed; instrumental Activities of Daily Living (ADL) are restricted to appropriate ages*.
3	Serious or medically significant but not immediately life-threatening; necessitating hospitalization or prolonged hospitalization; incapacity; self-care ADL are restricted**.

4	Fatal result: Urgent action is to be taken.
5	AE-related death

CTCAE = Common Terminology Criteria for Adverse Events

*: Instrumental ADL are activities such as cooking, grocery shopping, making/receiving phone calls, and financial management.

**: Self-care ADL are activities such as bathing, dressing and undressing, feeding yourself, going to the restroom, taking pills, and leaving the bed.

Attention must be paid to distinguish severity from intensity of an AE. "Severe" is used to describe intensity, so a severe AE is not definitely an SAE. For example, headache may appear severe in intensity but cannot be classified as an SAE, unless it meets the criteria for SAE.

4.7.3.2 Causality between the AE and the study drug

The investigator will evaluate whether causality between the study drug and the AE is "definitely related", "possibly related", "unlikely related", "definitely unrelated", or "not evaluable". Any AE without given causality to the study drug will be deemed as "possibly related" to the study drug.

- Definitely related:
  - Reasonable time relation+
  - In conformity with a known type of adverse reactions+
  - AE is absent or attenuated after interruption or dose reduction+
  - AE reoccurs after repeated medication+

5 Other reasonable interpretation-

- Possibly related:
  - Reasonable time relation+
  - In conformity with a known type of adverse reactions±?
  - AE is absent or attenuated after interruption or dose reduction±?
  - AE reoccurs after repeated medication±?
  - There is a probability of any other cause leading to this AE±?
- Unlikely related:

- Reasonable time relation-
- In conformity with a known type of adverse reactions-
- AE is absent or attenuated after interruption or dose reduction±?
- AE reoccurs after repeated medication±?
- There is a probability of any other cause leading to this AE±?

- Definitely unrelated:
  - -Reasonable time relation-
  - In conformity with a known type of adverse reactions-
  - AE is absent or attenuated after interruption or dose reduction-
  - AE reoccurs after repeated medication-
  - There is a probability of any other cause leading to this AE+
- Not evaluable: Essential data for evaluation is unavailable

Table 7. Evaluation of causality between AE and study drug

	Definitely Related	Possibly Related	Unlikely Related	Definitely Unrelated	Not Evaluable
Reasonable time relation with the study drug	＋	＋	－	－	Essential data for evaluation is unavailable
Known type of drug reactions	＋	±?	－	－	
Reaction is attenuated or absent after interruption	＋	±?	±?	－	
Reaction reoccurs after repeated medication	＋	?	?	－	
There is a probability of any other cause leading to this AE	－	±?	±?	+	
Note: ＋Yes －No ± Likely ? Unknown					

5.1.1 Determination of predictability

An unexpected AE refers to an event not in conformity with corresponding reference safety information (RSI) of the drug in nature or severity. For investigational medicinal products, the predictability of an AE will be assessed based on whether the event is listed in the Investigator's Brochure. For comparators that are already approved for marketing, the predictability of an AE will be assessed based on whether the event is listed in the drug instructions.

5.1.2 Reporting of SAEs

All SAEs occurring during the clinical study should be reported immediately (or in 24 h after being informed) by the investigator to the sponsor or a representative designated by the sponsor. This time frame applies to additional information (follow-up information) of previously released SAE report, and initial report and follow-up report of pregnant cases, too. The sponsor's representative and the investigator share the responsibility of ensuring that all essential information is submitted within the above time frame.

For all SAEs, the investigator is obliged to acquire relevant information and submit it to the sponsor within the above-mentioned time frame of reporting. In addition, the sponsor may request the investigator to acquire more follow-up information quickly. Such information may be more detailed than the information shown in the AE report. In general, such information shall include sufficiently detailed description of AEs so as to facilitate comprehensive medical assessment of the cases and independent assessment of causality. Moreover, the investigator must provide information about other potential causes of AEs, such as concomitant medications and complications.

In the event of subject death, a summary of autopsy findings (if any biopsy finding is available) has to be submitted to the sponsor or the representative designated by the sponsor as soon as possible.

Once the investigator or any other staff of the study site reports an AE as an SAE in the EDC system, an email will be automatically sent to alert the sponsor or the representative designated by the sponsor.

In the event of any fault occurring in EDC, a hard copy of completed and signed SAE report should be sent to the sponsor and the designated representative, and the study contact by fax/mail. In rare cases when no facsimile device is available, the event may be notified by phone, then a hard copy of SAE report can be sent by mail. After the investigator sends a notification by phone, it is still necessary for the investigator to complete and sign a hard copy of SAE report in 24 h after being aware of the event.

Information concerning contact among study sites for SAE reporting is detailed in investigator files provided to each study site. Each study site needs to keep original and fax confirmation pages (if a facsimile is used) of the SAE report along with the case report form.

Refer to the study-related Safety Management Plan (SMP) for details.

The sponsor is legally liable to inform local regulatory authority and other regulatory bodies of safety

information of the study drug. The investigator is legally obliged and ethically responsible to report promptly SAEs to relevant regulatory bodies and health authority, the ethics committee, and the study contact specifically in charge of receiving SAE reports, and make sure safety of other subjects is guaranteed.

The investigator or any person-in-charge required by local authority shall abide by local regulatory regulations on SAE reporting and report SAEs to regulatory bodies, Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

Refer to the study-related SMP for more details.

5.1.3 Follow-up of AEs

All AEs occurring in a period from signing Informed Consent Form through 90 days after the final dose of the study drug should be followed up until any of the following circumstances occurs:

1) The event is recovered (or returns to the baseline level);
2) The event is stable (as predicted by the investigator, the AE will not be further improved or exacerbated);
3) Failing to acquiring more information (the subject refuses to provide more information, or it is evidenced that the subject is lost to follow-up even after the maximum effort has been made).

The sponsor reserves a right to request (if necessary) more information of current AE/SAEs from any subject at the end of the study. After the subject withdraws from the study, the investigator has no longer any obligation of proactively collecting and reporting any new AE or SAE after the 90-day safety follow-up period. Nonetheless, if the investigator learns, after a subject has withdrawn from the study, that the subject experienced any SAE (including death) and reasonably considers that this event is possibly related to the study drug, then the investigator should report it to the sponsor's pharmacovigilance team or representative.

5.1.4 Pregnancy

Each fertile subject shall take appropriate contraceptive measures in a period from signing Informed Consent Form through at least 120 days after the final dose of the study drug and in at least 150 days after the final dose of chemotherapy drug.

Once becoming pregnant during the study, female subjects shall immediately discontinue the study drug and notify the investigator. The investigator shall report any pregnancy event to the sponsor (or an authorized representative) in 24 h after becoming aware of the pregnancy. Monitoring of the subject will persist until the end of pregnancy. Any pregnancy that occurs within 6 months after the final dose of the study drug should be reported to the investigator.

If any female subject or the spouse of any male subject gets pregnant during the treatment and within 6 months after the final dose of the study drug (whichever occurs first), the investigator should complete a Pregnancy Report in 24 h after becoming aware of the pregnancy, report to the sponsor (or an authorized representative), and record in eCRF to facilitate outcome follow-up. Any pregnancy event should be followed up until 30 days after the end of pregnancy.

Any AE/SAE occurring in a mother or newborn during pregnancy, such as natural abortion or induced abortion, birth defects or congenital malformation of newborns, malformation and anomalies of death fetuses, complications of mothers and newborns, etc., should be documented and reported according to "4.7.3 Documentation of AEs" and "4.7.5 Reporting of SAEs".

6 STATISTICAL METHODOLOGY

6.1 Sample Size Estimation

The randomization ratio for this study is 2:1. The sample size is estimated based on the assumption that the median progression-free survival (PFS) for treatment with placebo + chemotherapy (Carboplatin–Etoposide) is 5 months and the hazard ratio (HR) of (HLX10 + chemotherapy) group versus the control group is 0.7, and it is further assumed that when the enrollment period is 24 months and the whole study period is 29 months, to achieve a confidence level of 85% at an overall significance level $\alpha = 0.05$ (two-sided), at least 336 PFS events have to be observed. Considering a dropout rate of 20%, a total of 489 subjects (326 in treatment arm and 163 in control arm) need to be enrolled in the 2 arms.

6.2 Blinded Sample Size Re-estimation

It is planned in this study that, when the 320 subjects (about 2/3 of the number of subjects planned to

be enrolled) was enrolled under supervision of the Independent Data Monitoring Committee (IDMC), the sponsor will consider performing a blinded sample size estimation, and if the blinded overall median PFS is lower than the expected value, then the sponsor will communicate with PI and regulatory authorities about the necessary increase in the sample size (number of PFS events).

6.3 Statistical Analysis Sets

6.3.1 Intent-to-treat (ITT) set

The ITT set is defined as a set of all subjects randomized in this trial, and the ITT population will serve as the primary population of efficacy assessment in this study. ITT population will be analyzed based on treatment arms.

6.3.2 Per protocol set (PPS)

As a subset of the ITT set, the PPS consists of all randomized subjects undergoing at least one post-treatment tumor assessment without any major protocol deviation that impacts the primary efficacy significantly. The analysis based on the PPS will serve as a support of ITT analyses.

6.3.3 Safety set (SS)

The SS is defined as a set of all subjects receiving at least one dose of the study drug. The safety set is the primary population for safety endpoint analysis and will be analyzed based on treatment arms.

6.3.4 Pharmacokinetic set (PKS)

All subjects receiving at least one dose of HLX10 and having at least one post-dose concentration measurement at scheduled PK time points without any major protocol violation that may impact the PK assessment significantly. PKS will be used for PK analysis.

6.4 Interim Analysis and Final Analysis

An Independent Data Monitoring Committee (IDMC) will be formed for this study to conduct the interim analysis. In this study, one interim analysis is planned, in which O'Brien–Fleming-like α-spending function (Lan–DeMets approximation) is used to control the overall Type I error rate.

- The interim analysis of PFS is planned when 66% (approximately 222) of planned PFS events are observed, in which the safety and efficacy of the investigational drug will be evaluated. Based on the first interim analysis using O'Brien-Fleming α-spending function, α = 0.012 (two-sided).
- The final analysis of PFS will be performed when a target number of PFS events (approximately 336) are observed, and for final analysis the α is 0.046 (two-sided) based on the O'Brien-Fleming alpha spending function.

6.5 Statistical Analysis Methods

All statistical analyses will be performed using SAS9.2 (or later) statistical analysis software. For continuous variables, standard descriptive statistics include median, mean, standard deviation (SD), minimum, and maximum, while categorical variables include the quantity and percentage.
The detailed statistical analysis plan and methodology shall be elaborated in the Statistical Analysis Plan (SAP).

6.5.1 Demographics, medical history, and baseline characteristics

Demographic information, baseline profile data, medical history, and concomitant medications of all randomized subjects will be summarized using descriptive statistics depending on the randomization approach.

6.5.2 Medication compliance

The medication compliance data of the investigational product (HLX10 or placebo combined with Carboplatin–Etoposide) will be summarized using descriptive statistics in groups.

6.5.3 Efiicacy analysis

6.5.3.1 Analysis of primary efficacy endpoints

PFS (assessed by the IRRC as per RECIST v1.1): PFS is defined as a period from randomization initiation to the first documentation of PD or death regardless of causality (whichever occurs first). Data of subjects with neither PD nor death will be censored on the day of the final valid tumor evaluation. Data of surviving subjects not undergoing any tumor assessment during the study will be

censored on the day of randomization. Data of subjects who have no PD reported and initiate any antitumor therapy not specified in the protocol will be censored on the day of the last evaluable tumor assessment prior to the initiation of subsequent antitumor treatment. The between-group comparison of PFS is performed by a stratified log-rank test with the following stratification factors: Sex (male versus female), PD-L1 expression level (negative, positive, or unidentified), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years); stratified COX proportional risk model will be used to estimate HR and its 95% CI; the Kaplan Meier method will be used to estimate the median, and the Kaplan–Meier curve will be plotted.

6.5.3.2 Analysis of secondary efficacy endpoints

Overall survival (OS): Defined as a period from randomization through death regardless of causality. Data of patients without death record will be censored on the last known survival date. Data of patients not providing any follow-up information will be censored on the randomization day. The OS will be analyzed using the same method as that for primary efficacy endpoints.

PFS assessed by the investigator as per RECIST v1.1: Its statistical method is the same as that for primary efficacy endpoints;

Objective response rate (ORR) assessed by the IRRC and the investigator as per RECIST v1.1 separately: Defined as the percentage of subjects whose best overall responses are evaluated as complete response (CR) or partial response (PR). The stratified Cochran-Mantel-Haenszel (CMH) method is used to test the between-group variation in the ORR and to estimate the odds ratio and its 95% CI.

Duration of response (DOR): Defined as a period from the first documentation of response (CR or PR) through the first documentation of PD or death (whichever occurs first). The DOR will be analyzed only for patients whose best overall responses are evaluated as CR or PR. Data of patients not experiencing PD or death after achieving response will be censored on the day of the final tumor assessment; if no tumor assessment is performed after response achievement, then data of such patients will be censored on the day of tumor assessment when response is achieved. The Kaplan-Meier method is used to estimate the median and plot the Kaplan-Meier curve;

6.5.4 Safety analysis

AEs will be described according to MedDRA terms and graded according to CTCAE v4.03. Adverse events occurring during or after the first dose of study drug will be summarized by CTCAE grade. Treatment-emergent adverse events (TEAEs) and concomitant medications in the trial will be summarized separately by treatment arm. The clinical laboratory parameters, ECOG PS scores, vital signs, physical examination, and ECG will be summarized by the treatment group and study visit. Values observed and changes from baseline will be descriptively reported by visit in this trial.

6.5.5 Pharmacokinetic analysis and immunogenicity analysis

6.5.6 Serum drug concentration will be descriptively summarized by scheduled collection time, at the same time as samples collection to assess for the presence of ADA. The schedule of blood sampleing for PK and immunogenicity assessment is summarized in Table 6 The statistical method will be detailed in the SAP.Biomarker analysis

During the screening for this study, tumor tissues of subjects will be collected for assay of the PD-L1 expression level, MSI and TMB; blood samples of subjects will be collected for assay of the MSI and TMB. The primary objective is to assess the relations among the PD-L1 expression and MSI, TMB and efficacy.

6.5.7 Analysis of subject-reported outcome variables

The health status and self-perceived health of each patient will be documented in the form of EQ-5D-5L scale, EORTC QLQ-C30 scale, and EORTC QLQ-LC13 scale.
Descriptive statistics are based on the allocation for the scale scores, subscale scores, and individual scores at each visit and their changes from baseline. The analytical methods will be detailed in the SAP. Unless otherwise specified, PRO analysis of all data will be performed based on the ITT set.

7 ETHICS

7.1 Ethical Requirements

This trial shall be implemented in accordance with the GCP, Declaration of Helsinki, relevant regulations, and review comments of the Institutional Review Board.

The investigator shall ensure that this trial is reviewed and approved by a qualified institutional review board in compliance with GCP. Prior to the trial, the investigator shall submit the trial protocol, informed consent forms, and other essential documents to the Institutional Review Board for review and approval. The sponsor shall provide the study drug after receiving the approval from the Institutional Review Board. Meanwhile, the Institutional Review Board shall be informed of subsequent protocol amendments and SAEs occurring during the study that may impact the safety of subjects in the trial and preclude the subjects from study continuation. The investigator is obligated to report the trial progress to the Institutional Review Board. In addition, the investigator must timely submit copies of all correspondences with the Institutional Review Board to the sponsor. When reviewing and approving the trial protocol, the Institutional Review Board must verify the protocol title and number, indicate and date the reviewed protocol documents. In the event of any additional amendment to the trial protocol and the informed consent forms during the trial, an additional written approval shall be obtained from relevant authorities according to relevant regulations.

7.2 Informed Consent

The investigator must inform information about this trial in both oral and written manners. The subject has the right to know detailed information about this trial.

The informed consent forms (along with the trial protocol) must be reviewed and approved by the Institutional Review Board. If necessary, the investigator is obligated to explain the content of the informed consent form to each subject in a manner and wording understandable to the subject. The subject shall have enough time to read through before duly signing the informed consent form.

The final text of the informed consent form shall contain: the trial objective, processes and time frame of the trial, operational check, expected potential benefits and risks of the subject, informing the subject

of being probably assigned to any other group in the trial; treatment and corresponding compensation obtained by the subject in the event of any trial-related damage; principle of confidentiality for personal data of the subject, etc.

The informed consent form must be signed and dated by the subject, and the investigator implementing the informed consent process shall also sign and date the informed consent form. The informed consent form shall be made in duplicates, with the investigator and the subject holding one copy. Should any important new information related to the study drug be found, the informed consent form has to be revised in writing and submitted to the Institutional Review Board for approval before being approved by the subject again.

7.3 Confidentiality for the Subject

The investigator is obligated to keep the subject anonymous. In the Case Report Form or other documents, the subjects can be only identified with capitalized letters, numbers and/or codes, instead of names. The investigator must properly keep the Subject Enrollment Log documenting the codes, names, and residential addresses of the subjects. The investigator must keep strictly confidential any document that may reveal the identity of the subject.

8 DATA MANAGEMENT

8.1 Database Setup

Data of this clinical trial will be collected through remote data entry in the eCRF. The data administrator shall design a database and test it with simulation data or real eCRF data to ensure that the database is accurate and correct.

8.2 Data Checks

During data management, data checks include the edit check, manual check, medical check, and statistical pre-analysis check. All the data query will be displayed in the EDC system in the form of electronic query for the study site to answer. The query will be closed if the answer is acceptable. If any data query is not resolved or a new query arises after the database is updated based on the answer

to the previous data query, then the investigator or CRC shall answer again. The above process will be repeated until all data in the database is checked to be correct.

8.3 Database Lock

The data administrator shall draft a data review report pursuant to the trial protocol, data review criteria, and the database. The project manager shall convene a data review meeting attended by the sponsor, principal investigator, statistician, and data administrator to review the data, and a data review resolution shall be jointly signed by the representatives of the participants. The data administrator shall implement data locking upon approval by all the participants. The locked data will be submitted to the statistician for statistical analysis.

The data can be locked when the following conditions are satisfied.

1) All data has been collected and entered into the database.
2) All codes have been checked and verified.
3) All data queries have been resolved (including queries proposed in data review).
4) Data review has been completed.
5) Source data verification has been completed.
6) Verification of SAEs has been completed.
7) Signatures of all investigators have been obtained.
8) Analyzable cases have been defined and stored in the final analysis database.
9) The SAP has been signed.

9 STUDY MANAGEMENT

9.1 Quality Control and Quality Assurance

Prior to the formal initiation of the trial, the sponsor (or CRO authorized by the sponsor) and the investigator shall discuss and develop a clinical study plan to guarantee the trial quality. The study personnel involved in this trial shall be trained on GCP.

Study drugs must be managed in each study site as per relevant SOPs, which involve the receipt, retention, distribution, and recovery of the drugs.

In accordance with the GCP guideline, necessary steps must be taken during the design and

implementation of this study to ensure the accuracy, consistency, integrity, and credibility of the collected data. All observations and outliers in the clinical trial shall be promptly and carefully verified and recorded to ensure data reliability. Ensure that various instruments, devices, reagents, and reference standards in this clinical trial are in strict compliance with corresponding quality specifications and operate in the normal state.

The investigator will enter information required by the protocol into the Case Report Form, and the monitor shall check if it is completely and accurately filled out and instruct the personnel in the study site to make amendments and supplements if necessary.

The drug regulatory authorities and the sponsor may authorize auditors to conduct systematic examination of activities and documents in connection with the clinical trial, so as to evaluate if the trial is carried out in accordance with the trial protocol, SOPs and relevant regulatory requirements, and if the trial data is documented in a timely, authentic, accurate, and complete manner. The audit shall be performed by personnel not directly involved in this clinical trial.

9.1.1 Training

According to the GCP guideline, the CRA shall have the qualification accepted by the sponsor; before the clinical trial, the person in charge of the study site shall train the investigator on the trial protocol, so as to enable the investigator to become fairly familiar with this clinical trial protocol, master the GCP guideline, unify the documentation approach and evaluation criteria, and perform the trial in strict accordance with the protocol.

9.1.2 Clinical monitoring

The CRA is a primary liaison between the sponsor and the investigator. The CRA will fulfill all monitoring responsibilities to monitor this clinical study in accordance with GCP. The CRA will establish and maintain regular contact between the investigator and the sponsor.

The CRA will conduct regular clinical monitoring according to all relevant regulatory requirements and standards, or visit the study site depending on actual situation, push the progress of the clinical trial, check and verify if all data records and reports, and eCRF entries are correct and complete, and

consistent with the source data, and ensure that the clinical trial is performed according to the clinical trial protocol; the investigator shall actively assist the CRA in these processes.

9.1.3 Audit

During the study, the sponsor may conduct a QA audit for the study site, the study database, and the study documentation. The audit includes drug supply, required trial documents, documentation of the informed consent process, and consistency between the Case Report Form and source documents, and so on. The content and scope of the audit can be added when needed. After being reasonably notified, the investigator shall accept the study-related audit by the auditors authorized by the sponsor, as well as the inspection by regulatory authorities.

In addition, the regulatory authorities may inspect the study as well.

9.1.4 Data management

The departments of data management and biostatistics will process data generated in this clinical study according to relevant SOPs.

Data acquisition is performed by the personnel from a study site designated and authorized by the investigator. Before the study is initiated and any data of any subject in the study is entered into the EDC system, the investigator and all the personnel from the authorized study site must be trained properly, and appropriate safety measures shall be taken.

The monitor will compare the eCRF with source documents to ensure that there is no deviation between crucial data. All items, corrections, and changes have to be completed by the investigator or the personnel designated by the investigator. Relevant personnel of the study will raise queries and send to the investigator. In this regard, the EDC will be audited and tracked, which means the names of the study personnel, time, and date will be documented.

The investigator is responsible for maintaining source documents. These documents shall be checked by the monitor of the study during each monitoring visit. The investigator must submit one copy of complete eCRF including data of every subject receiving study medication, regardless of the treatment duration of the subject. The study and subject numbers shall be used to indicate explicitly all supporting documents submitted along with the eCRF, e.g., laboratory or hospital records. Any personal

information including subject names shall be deleted or made illegible so as to keep the subject information confidential.

9.1.5 Missing and useless data

The processing procedures for missing and useless data are detailed in the SAP.

9.2 Documentation and Retention of Study Data

The investigator is obligated to maintain essential documents of the study (the protocol and protocol amendment, completed eCRFs, signed informed consent forms, important correspondence files, and all other supportive documents). The study site shall establish a plan to retain these documents for 5 years after study completion. The study site shall always retain these documents until at least 2 years after the investigational product is finally approved for marketing, and until at least 5 years after there is no pending approval or marketing authorization application for the investigational product, or after clinical development of this investigational product is formally terminated. These documents shall be retained for a longer time upon the request of any corresponding regulatory authority, or any hospital, institution, or private clinic involved in this study. Subject codes (subject names and corresponding study numbers) should also be retained for the same time period. As agreed by the sponsor, these documents can be transferred to another responsible party who must observe the document retention policy. The sponsor must be notified in writing of any transfer of documents. The investigator must contact the sponsor before disposing of any study record.

9.3 Follow-ups and Medical Measures After Study Completion

Unresolved AEs/SAEs (including laboratory outliers) when the study is completed or any subject withdraws from the study prematurely have to be followed up, as detailed in "4. AEs and SAEs".
After study medication is completed, the investigator shall take necessary and reasonable medical measures for the subjects to safeguard the safety, rights and interests of the subjects.

10 RESPONSIBILITIES

10.1 Responsibilities of the Investigator

The investigator's responsibilities mainly include but are not limited to:

1) Designing and signing a trial protocol with the sponsor through discussion, and reporting the protocol to the Institutional Review Board for approval before implementation.
2) Scrutinizing, understanding, and strictly implementing the protocol.
3) Being knowledgeable about and familiar with the nature, function, efficacy, and safety of the investigational product (including information about the preclinical study for the product), as well as all new information related to the product discovered during the clinical trial.
4) Conducting the clinical trial in medical institutions equipped with adequate medical facilities, laboratory equipment, and staffing, as well as all facilities needed to handle emergencies to ensure the safety of the subjects. Ensuring the laboratory results are accurate and reliable.
5) Obtaining the consent of the medical institution or the competent authority, and ensuring that sufficient time is left to complete the clinical trial within the time limit set by the protocol. Explaining the data, regulations, and responsibilities concerning the trial to all staff participating in the clinical trial to ensure that a sufficient number of subjects meeting the requirements of the protocol are enrolled in the clinical trial.
6) Explaining to the subjects the details of the trial approved by the Institutional Review Board and obtaining the Informed Consent Form from the subjects.
7) Making medical decisions related to the clinical trial to ensure that the subjects receive appropriate treatment in case of adverse events during the trial.
8) Taking necessary measures to ensure the safety of the subjects and putting on record such measures. Taking immediate and appropriate treatment measures for the subjects in case of any serious adverse events during the clinical trial, reporting the serious adverse event to the drug regulatory authorities, health administrative departments, the sponsor and the Institutional Review Board, and making sure to sign and date the report before submission.
9) Ensuring that data is recorded in the case history and the Case Report Form in a true, accurate, complete, timely, and legitimate manner.

10) Accepting the monitoring and audit by the monitors and auditors dispatched by the sponsor, as well as the audit and inspection by the drug regulatory authorities to ensure the quality of the clinical trial.
11) Discussing with the sponsor the cost of the clinical trial and including it in the contract. Refraining from charging the subjects for the cost of the investigational product during the clinical trial.
12) Writing, signing, and dating a final report after the clinical trial is complete, and sending it to the sponsor.

10.2 Responsibilities of the Sponsor

The sponsor's responsibilities mainly include but are not limited to:

1) Obtaining approval from the China Food and Drug Administration (CFDA).
2) Initiating and applying for a clinical trial, as well as funding the trial.
3) Providing an Investigator's Brochure covering the chemical, pharmaceutical, toxicological, pharmacological, and clinical (including previous and ongoing trials) information and data for the investigational product.
4) Designing a clinical trial protocol jointly with the investigator. Signing the trial protocol and contract agreed upon by both parties.
5) Providing the investigator with an investigational product and a comparator that are easy to identify, correctly coded, and specially labeled, while guaranteeing the quality of the investigational product and the comparator. Packaging and storing the investigational product properly as required by the trial protocol. Establishing a management system and recording system for the investigational product.
6) Appointing qualified monitors who are accepted by the investigator.
7) Establishing a quality control and quality assurance system for the clinical trial, and organizing audits for the clinical trial to ensure its quality.
8) Working with the investigator to promptly study the serious adverse events that have occurred and taking necessary measures to ensure the safety and rights of the subjects. Reporting the serious adverse events to the drug regulatory authorities and health administrative departments in a timely manner.

9) Submitting a final report of the trial to the China Food and Drug Administration (CFDA).
10) Purchasing the liability insurance for this drug clinical trial. Providing comprehensive medical coverage for the subjects of the clinical trial, and bearing the cost of the treatment and corresponding financial compensation for the subjects experiencing injuries or deaths associated with the trial. Providing the investigator with legal and economic guarantees, except for those caused by medical malpractice.

11 CONFIDENTIALITY AND PUBLICATION OF TRIAL RESULTS

All information about the trial (including but not limited to the following documents: the protocol, and the Investigator's Brochure) is the intellectual property of the sponsor and may not be disclosed to any third party not related to the trial. The investigator must recognize that the scientific or medical information obtained from this trial may be of commercial value to the sponsor. The investigator shall keep the information and data related to this trial confidential. If the investigator intends to publish the information related to this trial or the conclusions drawn from the trial, the investigator shall negotiate with the sponsor in advance and obtain the written consent of the sponsor. In order to protect its rights, the sponsor may request the investigator not to publish information related to the trial before the trial product is approved for marketing.

The sponsor has the right to publish or release information or data related to the trial or to report it to the drug administrative departments. If the sponsor needs to display the name of the investigator in the content published, released, or advertised, the sponsor shall obtain the consent of the investigator.

12 REFERENCE

[1] Siegel R L , Miller K D , Jemal A . Cancer statistics, 2018.[J]. Ca A Cancer Journal for Clinicians, 2018, 60(5):277-300.

[2] 陈万青, 孙可欣, 郑荣寿, et al. 2014 年中国分地区恶性肿瘤发病和死亡分析[J]. 中国肿瘤, 2018, 27(1):1-14.

[3] Eskandar A, Ahmed A, Daughtey M, et al. Racial and sex differences in presentation and outcomes of small cell lung cancer in the United States: 1973 to 2010[J]. Chest, 2015,147(4): e164-e165.

[4] Klautke G , Sauer R , Fietkau R . Combined Treatment Modality in Small Cell Lung Cancer[J]. Strahlentherapie Und Onkologie, 2008, 184(2):61-66.

[5] Kurup A, Hanna NH. Treatment of small cell lung cancer[J]. Crit Rev Oncol Hematol, 2004, 52: 117-126.

[6] 彭红. 肺癌住院病例的流行病学特征及预后随访研究[D]. 上海: 复旦大学, 2010.

[7] Puglisi M , Dolly S , Faria A , et al. Treatment options for small cell lung cancer – do we have more choice?[J]. Br J Cancer, 2010, 102(4):629-638.

[8] Puglisi M , Dolly S , Faria A , et al. Treatment options for small cell lung cancer – do we have more choice?[J]. Br J Cancer, 2010, 102(4):629-638.

[9] Ishida Y , Agata Y , Shibahara K , et al. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death[J]. Embo Journal, 1992, 11(11):3887-3895.

[10] Stadler S, Weina K, Gebhardt C, et al. New therapeutic options for advanced non-resectable malignant melanoma[J]. Adv Med Sci, 2015, 60(1):83-88.

[11] Basso D,Fogar P,Falconi M,et al.Pancreatic tumors and immature immunosuppressive myeloid cells in blood and spleen：role of inhibitorv co-stimulatorv molecules PDLl and CTLA4.An in vivo and in vitro study[J] .PLOSONE, 2013, 8(1) :e54824.

[12] Chen S, Liu H, Su N, et al. Myeloid-derived suppressor cells promote age-related increase of lung cancer growth via B7-H1[J]. Experimental Gerontology, 2015, 61:84-91.

[13] Keir, M. E. Tissue expression of PD-L1 mediates peripheral T cell tolerance[J]. Journal of Experimental Medicine, 2006, 203(4):883-895.

[14] Dong H, Strome S E, Salomao D R, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion[J]. Nature Medicine, 2002, 8(8):793-800.

[15] Nishizumi H . Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor[J]. Immunity, 1999, 11(2):141-151.

[16] Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application[J]. International Immunology, 2007, 19(7):813-824.

[17] Yokosuka T, Takamatsu M, Kobayashiimanishi W, et al. Programmed cell death 1 forms negative costimulatory microclusters that directly inhibit T cell receptor signaling by recruiting phosphatase SHP2[J]. Journal of Experimental Medicine, 2012, 209(6):1201-1217.

[18] Sheppard K A , Fitz L J , Lee J M , et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3ζ signalosome and downstream signaling to PKCθ[J]. Febs Letters, 2004, 574(1-3):0-41.

[19] Patsoukis N, Brown J, Petkova V, et al. Selective Effects of PD-1 on Akt and Ras Pathways Regulate Molecular Components of the Cell Cycle and Inhibit T Cell Proliferation[J]. Science Signaling, 2012, 5(230):ra46.

[20] Merritt RE, Mahtabifard A, Yamada RE, et al. Cisplatin augments cytotoxic T-lymphocyte-mediated antitumor immunity in poorly immunogenic murine lung cancer[J]. The Journal of Thoracic and Cardiovascular Surgery, 2003; 126:1609-17.

[21] Apetoh L , Ghiringhelli F , Tesniere A , et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy.[J]. Nature Medicine, 2007, 13(9):1050-1059.

13 APPENDICES

Appendix 1: Common Terminology Criteria for Adverse Events

This study will report AE using CTCAE v4.03. CTCAE v4.03 can be downloaded from the home page of the Cancer Therapy Evaluation Program (CTEP). CTCAE v4.03 shall be used in all relevant study sites. The URL is as follows:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix 2-1: Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

The following is the Response Evaluation Criteria in Solid Tumors RECIST Version 1.1. For more details, please refer to the English version at http://ctep.cancer.gov/protocolDevelopment/docs/ recist_guideline.pdf.

Method

- Currently, CT and MRI are the best reproducible methods used for assessing the response of selected target lesions. The lesion on the CT scan is measured according to the following assumption: CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be at least twice the slice thickness. The use of MRI to assess diseases throughout the entire study is acceptable.
- Through the entire trial, the same assessment method and the same technique are used to characterize each identified and reported lesion.
- Ultrasound diagnosis (US) shall not be used to measure objective tumor response or progressive disease. For this study protocol, cross sectional imaging techniques (CT or MRI) are used to assess complete responses, partial response, or stable disease. FDG-PET examination is not suitable for assessing tumor response. It is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progressive disease. To determine progressive disease (PD), new lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
    1) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
    2) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

If the investigator decides to use combined PET-CT, the CT portions of PET-CT shall not be substituted for dedicated CT examination required by this study protocol to complete the RECIST measurement, unless the research institute may confirm that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Cytology and histology can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors

can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

The definitions of "measurable" and "non-measurable" tumors:

All measurements should be recorded in metric notation, using rulers or calipers. Measurement results shall be recorded in a single dimension. At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

- Measurable: The tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm). When the CT scan slice thickness is greater than 5 mm, the longest diameter of the measurable lesion shall be at least 10 mm or twice the slice thickness. Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan.
- Non-measurable: All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions, that are characterized as non-target lesions. Lesions considered truly non-measurable include: bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

  Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules and tangible lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. Lesions which cannot be accurately measured with calipers should be recorded as non-measurable.

Special considerations regarding lesion measurability:

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components (that can be evaluated by cross sectional imaging techniques such as CT or MRI) can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic lesions: Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions. "Cystic lesions" is thought to represent cystic metastases that can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Baseline (i.e., before treatment) documentation of "target" and "non-target" lesions

During treatment, a maximum of five 5 target lesions are selected for measurement (a maximum of two lesions per organ). Target lesions shall be selected according to their size and the appropriateness of reproducible repeated measurements using imaging techniques or clinical means.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- All other lesions (or affected sites; including any measurable lesions or pathological lymph nodes not selected as target lesions) shall be identified as non-target lesions. Non-target lesions shall be recorded and qualitatively assessed during treatment. Measurements are not required and these lesions should be followed as "present", "absent", or in rare cases "unequivocal progression".
- Bone lesions: Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. If a sign or symptom indicative of bone metastases is present, a bone scan, MRI, CT, PET, PET/CT, or X-ray scan shall be performed. For subjects who are positive for bone scans or PET scans, another imaging technique (e.g., X-ray, CT, or MRI) must be used to confirm bone metastasis.

<u>Response criteria</u>

A subject's tumor response is assessed based on the response for target and non-target lesions, as well as the appearance of new lesions and disappearance of old lesions.

Evaluation of target lesions

*Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10 mm.
*Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
*Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
*Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while in

	study.
Not Applicable (NA):	No target lesions are identified at baseline.
Not Evaluable (NE):	The scan is not completed, the scan result is incomplete, or the scan is not evaluated due to poor quality of the scan at the time point chosen for the evaluation of target lesions.

*Diameter to be used:

For lymph node lesions: the shortest axis

For non-lymph node lesions: the sum of longest diameters

Once the study is started, the following rule will be adopted: If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If the size of the lesion increases to 5 mm or more in one direction, their actual diameter shall be recorded. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm in study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. In order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis)
Non-CR/non-PD:	Persistence of one or more non-target lesion(s)
Progressive Disease (PD):	Appearance of one or more new lesions, or if the original non-target lesions show suspicious progression.
Not Applicable (NA):	No non-target lesions are identified at baseline.
Not Evaluable (NE):	The scan is not completed, the scan result is incomplete, or the scan is not evaluated due to poor quality of the scan at the time point chosen for the evaluation of non-target lesions.

When the patient also has measurable disease, in this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease. Even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. When the patient has only non-measurable disease, the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease (which is equivalent to a 20% increase in the sum of diameters in all measurable lesions).

Evaluation of best overall response

The status of the overall response of subjects at various time points is calculated as follows:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable

Time point response of patients with non-target disease only.

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
NE	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
A "Non-CR/Non-PD" is preferred over "stable disease" for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.		

Special notes on response assessment

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". In this case, it is not possible at this time to use "progressive disease" as an overall objective response of the tumor. Every effort should be made to document objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled

assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurement recorded in study).

Appendix 2-2: Modified Response Evaluation Criteria in Solid Tumors

Modified Response Evaluation Criteria in Solid Tumors

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiological progression, including the appearance of new lesions. Therefore, modified response criteria have been developed that account for the possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment.

Modified Response Evaluation Criteria in Solid Tumors (RECIST) is derived from RECIST version 1.1 conventions [1,2,3] and immune-related response criteria[3,4,5] (irRC). The provisions of RECIST v1.1 are adopted unless otherwise specified.

Modified RECIST and RECIST, Version 1.1: Summary of Changes

	RECIST v1.1	Modified RECIST
New Lesions After Baseline	Define progression	New measurable lesions are added into the total tumor burden and followed.
Non-Target Lesions	May contribute to the designation of overall progression	Only contribute to the assessment of a complete response
Radiographic Progression	First instance of ≥20% increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease

RECIST = Response Evaluation Criteria in Solid Tumors.

A. Definitions of Measurable/non-Measurable Lesions

All measurable and non-measurable lesions should be assessed at screening and at the protocol-specified tumor assessment time points. Additional assessments may be performed, as clinically indicated for suspicion of progression.

A.1 Measurable Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥

15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

A.2 Non-Measurable Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with short axis ≥10 but <15 mm), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

A.3 Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions

Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-osteogenic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Osteogenic bone lesions are non-measurable.

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment

Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

B. Tumor Response Evaluation

B.1 Definition of Target/Non-Target Lesions

Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites),

respectively, will be recorded. Other lesions in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance, the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention because they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis of <10 mm are considered non-pathological and need not to be recorded or followed.

Lesions irradiated within 3 weeks prior to Cycle 1, Day 1 may not be counted as target lesions.

Non-Target Lesions

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required.

It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

After baseline, changes in non-target lesions will contribute only to the assessment of complete response (i.e., a complete response is attained only with the complete disappearance of all tumor lesions, including non-target lesions) and will not be used to assess progressive disease.

New Lesions

During the study, all new lesions identified and recorded after baseline must be evaluated at all tumor assessment time points. The measurability of new lesions must also be assessed in the same manner with the prospective evaluation criteria for target lesions (according to RECIST) used at baseline (e.g., non-lymph node lesions must be ≥10 mm; see note for new lymph node lesions). A maximum of five lesions total (and a maximum of two lesions per organ) are measured at all time points and are included in the tumor response evaluation. According to RECIST criteria, new-type lesions that are not target lesions are not included in the tumor response evaluation.

Thereafter, if there are less than five new measurable lesions, new lesions that are not measurable in the first instance but meet the measurability criteria at subsequent follow-up time points can be included in the sum of longest diameters (SLD).

B.2 Calculation of Sum of the Diameters

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as a measure of tumor burden.

The sum of the diameters is calculated at baseline and at each tumor assessment for the purpose of classification of tumor responses.

Sum of the Diameters at Baseline: The sum of the diameters for all target lesions identified at baseline prior to treatment on Day 1.

Sum of the Diameters at Tumor Assessment: For every on-study tumor assessment collected per protocol or as clinically indicated, the sum of the diameters at tumor assessment will be calculated using tumor imaging scans. All target lesions and all new measurable lesions (a maximum of five lesions total and a maximum of two lesions per organ) that have emerged after baseline will contribute to the sum of the diameters at tumor assessment. Hence, each net percentage change in tumor burden per assessment with use of modified RECIST accounts for the size and growth kinetics of both old and new lesions as they appear.

Note: If new lymph nodes appear, its evaluation must be carried out following RECIST v1.1 for measurable lesions (equivalent to the selection of baseline target lesions). If the short diameter of a newly appeared lymph node lesion is ≥15 mm, it is considered as a new measurable lesion, and is followed up and included in the SLD. Thereafter, lymph node lesions are measured at subsequent time points and the results are included in the SLD, even if the short diameter shrinks to <15 mm (or even to <10 mm). However, if the diameter shrinks to <10 mm at subsequent time points and all other lesions cannot be detected (or if the short diameter of the lymph nodes shrinks to <10 mm), the result of response evaluation is CR.

If the short diameter of a newly appeared lymph node lesion is ≥10 mm and <15 mm, the lymph node is not measurable but is still considered as a new lesion. This lesion will not be included in the SLD unless it becomes measurable later (short diameter ≥15 mm).

If the new lymph node is <10 mm in diameter, it is not considered as a pathological lesion and is not considered as a new lesion.

B.3 Response Criteria

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Complete response (CR): Disappearance of all target lesions. Lymph nodes that shrink to <10 mm short axis are considered normal.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of all target and all non-target

measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR.

Note: The appearance of new measurable lesions is factored into the overall tumor burden but does not automatically qualify as progressive disease until the sum of the diameters increases by ≥20% when compared with the sum of the diameters at nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the diameters while in the study.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and all new measurable lesions, taking as reference the smallest sum in study (minimum SLD; this includes the baseline sum if that is the smallest in study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Impact of New Lesions on Modified RECIST

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is included in the sum of the diameters, which is used to determine the overall modified RECIST tumor response.

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Table 1. Modified RECIST Time Point Response Definitions

% Change in Sum of the Diameters[a]	Response Evaluation of Non-Target Lesions	Overall Modified RECIST Time Point Response
Compared with the baseline period: –100%[b]	CR	CR
Compared with the baseline period: –100%[b]	Non-CR or not all evaluated	PR
Compared with the baseline period: ≤ –30%	Any	PR
> –30% to < +20%	Any	SD
Not all evaluated	Any	NE
Compared with minimum SLD: ≥ +20%	Any	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; SLD = sum of longest diameters.

[a] % change in sum of the diameters (including measurable new lesions when present)

[b] When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met because a normal lymph node is defined as having a short axis of = 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm in order to meet the definition of CR.Appendix 3:Quality of Life Scale EORTC QLQ-C30, EQ-5D-5L, EORTC QLQ-LC13

EORTC QLQ-C30 (3rd Edition)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4

13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall <u>health</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall <u>quality of life</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EQ-5D-5L Health Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY.

14 MOBILITY

I have no problems in walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑

15 SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

16 PAIN / DISCOMFORT

I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

17 ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

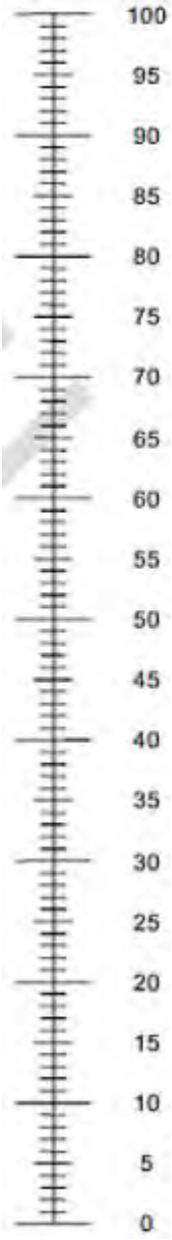
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine. 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

The best health you can imagine

YOUR HEALTH TODAY = ☐

The best health you can imagine



The worst health you can imagine

EORTC QLQ- LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Annex 4: Eastern Cooperative Oncology Group (ECOG) - Performance Status Scale

Score	ECOG Status
0	Mobility is completely normal, and there is no difference before and after the onset of the disease.
1	Free to walk and engage in light physical activities, including general housework or office work, but not heavy physical activities.
2	Able to walk and independently take care of oneself, but cannot do any work. Able to get up and move around for at least half of the time during the day.
3	Able to only finish some of self-care activities and spend more than half of the time during the day in bed or in a wheelchair.
4	Complete disability. Cannot take care of oneself at all. Totally confined to bed or in a wheelchair.
5	Death

ECOG = Eastern Cooperative Oncology Group

Appendix 5: Fridericia Correction Formula

Fridericia formula: $QTc=QT/RR^{0.33}$

Appendix 6: Cockcroft and Gault Formula

The creatinine clearance rate is calculated using the measured value of serum creatinine (unit: mL):

Male: $$\frac{(140-\text{age}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72}$$

Female: $$\frac{(140-\text{age}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72} \times 0.85$$

Cited from Cockcroft DW et al. Nephron. 1976; 16(1): 31-41.

The creatinine clearance rate is calculated using the measured value of serum creatinine (unit: μmol/L):

Male: $$\frac{(140-\text{age}) \times \text{weight (kg)} \times 1.23}{\text{creatinine (μmol/L)}}$$

Female: $$\frac{(140-\text{age}) \times \text{weight (kg)} \times 1.23 \times 0.85}{\text{creatinine (μmol/L)}}$$

Cited from Cockcroft DW et al. Nephron. 1976;16(1):31-41.

Appendix 7: Heart Functional Classification of New York Heart Association

Grade	Behavioral Status
Grade I	Physical activities are not restricted. Normal physical activities do not cause excessive fatigue, palpitations or breathing difficulties
Grade II	Physical activities are slightly restricted and the patient feels comfortable at rest. However, normal physical activities can cause fatigue, palpitations or difficulty breathing
Grade III	Physical activities are significantly restricted. The patient feels comfortable at rest. However, activities lighter than normal physical activities can cause fatigue, palpitations or difficult breathing
Grade IV	Unable to perform any physical activity comfortably. Symptoms of cardiac insufficiency can occur even at rest. Any physical activity can aggravate discomfort.

Appendix 8: Guidelines for Dose Modification and Treatment for Immune-Related Toxicity

<table>
<tr><th colspan="2">Dose Modification</th><th>Toxicity Treatment</th></tr>
<tr><td colspan="2">Based on the severity of the toxicity caused by drug administration (according to NCI CTCAE v4.03 classification), adjustment will be made to the administration of the study drug/study protocol to manage potential immune-related AEs.
In addition to the criteria for permanently discontinuation of the study drug/study protocol based on CTC grade/severity (listed below), the study drug/study protocol is permanently discontinued if:
• After the last dose of study drug/study protocol, the dose of corticosteroids cannot be reduced to prednisone ≤10 mg/day (or an equivalent dose of other medications) within 12 weeks
• Recurrence of pre-existing grade 3 TEAE after the resumption of treatment</td><td rowspan="4">It is recommended that the treatment of irAE shall follow the guidelines described in this table.
− Subjects shall be fully evaluated to rule out any other possible causes (e.g., progressive disease, concomitant medication, and infection).
− In the absence of a clear cause other than immune-related causes, all events shall be considered as potentially immune-related.
− For low-grade (grade 1 or 2, unless otherwise stated) events, symptomatic and topical treatments shall be considered.
− For sustained (>3-5 days) low-grade (grade 2) or severe (≥3) adverse events, patients shall be immediately treated with prednisone PO 1-2 mg/kg/day or IV administration of an equivalent dose of other medications
− If the symptoms recur or worsen during the gradual dose reduction of corticosteroids (during a 28-day period of dose reduction), the dose of corticosteroids shall be increased (the dose of prednisone (e.g., up to 2-4 mg/kg/day or IV administration of an equivalent dose of other medications)) until the symptoms</td></tr>
<tr><td>Grade 1</td><td>No dose adjustment is required</td></tr>
<tr><td>Grade 2</td><td>Suspend the administration of study drug/study protocol until grade 2 response is relieved to ≤ grade 1.
If the toxicity is aggravated, treatment is performed according to those suitable for grade 3 or grade 4 responses.
Once the dose of steroids is gradually reduced and the event is stabilized to ≤ grade 1, the study drug/study protocol can be resumed.
For patients with endocrine disorders who may require long-term or sustained steroid replacement therapy, they may resume the treatment of the study drug/study protocol under the following conditions:</td></tr>
</table>

<table>
<tr><td></td><td>1. The event has become stabilized and controlled.
2. The subject is clinically stable according to the judgment of the investigator or attending physician.
3. The dose of prednisone or an equivalent dose of other medications is ≤ 10 mg/day.</td><td rowspan="4">stabilize or improve, then the dose of corticosteroids shall be decreased at a slower rate (> 28 days).
− For events that did not response to systemic steroids, a more potent immunosuppressive agent shall be considered, such as a TNF inhibitor (e.g., infliximab) (for specific types of immunosuppressive agents, please refer to various sections of irAE).
− For grade 3/4 inflammatory responses (e.g., inflammatory responses to metastatic lesions and lymph nodes) caused by local tumor responses, there is no need for compulsory discontinuation of study drug/study treatment. Whether or not to continue the use of the study drug in this case shall be determined based on the patient's benefit/risk analysis.</td></tr>
<tr><td>Grade 3</td><td>Based on individual toxicity, the study drug/study protocol may be permanently discontinued. Please refer to the guideline below.</td></tr>
<tr><td>Grade 4</td><td>Permanent discontinuation of the study drug/study protocol.</td></tr>
<tr><td colspan="2">Note: The study drug/study protocol is suspended for asymptomatic amylase or lipase elevation at grade 3 and above. If a complete examination does not suggest evidence of pancreatitis, the study drug/study protocol can be resumed or restarted.</td></tr>
<tr><td colspan="4">Immune-Mediated Response</td></tr>
<tr><td>Adverse Events</td><td>Seriousness of Adverse Events (NCI CTCAE Version 4.03)</td><td>Administration Adjustment</td><td>Toxicity Management</td></tr>
<tr><td>Pneumonia/ILD</td><td>All grades</td><td>General guidelines</td><td>For immune-mediated response of all grades:
− Subjects are monitored for signs and symptoms of pneumonia or ILD (new or aggravated episodes of shortness of breath or cough). Subjects shall be assessed using imaging and pulmonary function examinations, including other diagnostic procedures described below.
− Initial examinations may include clinical evaluation, monitoring of oxygenation (oxygenation during rest</td></tr>
</table>

			and activity) by a pulse oximeter, laboratory examinations, and high-resolution CT scans.
	Grade 1 (asymptomatic, only with results of clinical or diagnostic observations, no indication for intervention)	No administration adjustment is required. However, during the etiological diagnosis, it may be necessary to suspend the administration of the study drug/study protocol depending on the clinical situation.	For grade 1 (with changes in imaging results only): − Clinical symptoms, pulse oximetry (oxygenation during rest and activity) and laboratory tests shall be monitored and closely followed within 2 to 4 days, followed by further monitoring and follow-up based on clinical indications. − A consultation with the departments of respiration and infectious diseases can be considered.
	Grade 2 (With symptoms, indications for medical intervention, and limited instrument activities of daily living)	Suspend the administration of study drug/study protocol until grade 2 response is relieved to ≤ grade 1. • If the toxicity is aggravated, treatment is performed according to those suitable for grade 3 or grade 4 responses. • If the toxicity is improved to ≤ grade 1, the resumption of the study drug/study protocol will be determined based on the clinical judgment of the attending physician after the dose reduction of steroids is completed.	For grade 2 (mild to moderate new symptoms): − Monitor symptoms daily and consider hospitalization. − Immediately start the treatment with systemic steroids (e.g., prednisone 1-2 mg/kg/day PO or IV administration of an equivalent dose of other medications). − Imaging examinations are performed again according to clinical indications. − If there is no improvement within 3-5 days, additional examination shall be considered along with an immediate treatment with IV methylprednisolone 2-4 mg/kg/day. − If there is still no improvement within 3-5 days after the treatment with IV methylprednisolone 2-4 mg/kg/day, an immunosuppressive treatment, such as the use of a TNF inhibitor (for example, infliximab

			5mg/kg, once every 2 weeks), shall be started immediately. Note: It is important to rule out sepsis and refer to the general instructions of infliximab for use. − Once there is improvement, steroids are gradually reduced for ≥ 28 days. In addition, prophylactic use of antibiotics, anti-fungal or anti-PCP agents shall be considered (refer to current NCCN guidelines for the treatment of cancer-related infections (category 2B recommendations))[a]. − A consultation with the departments of respiration and infectious diseases can be considered. − Consider to discuss with the physician if necessary.
	Grade 3 or 4 (Grade 3: severe symptoms; limited self-care ability in activities of daily living; indication for oxygen inhalation) (Grade 4: life-threatening respiratory failure requiring urgent intervention (e.g., tracheotomy or intubation))	Permanent discontinuation of the study drug/study protocol.	For grade 3 or 4 (severe or new symptoms, new hypoxia/aggravated hypoxia, life-threatening): − Immediately start the empiric treatment with methylprednisolone 1-4 mg/kg/day or IV administration of an equivalent dose of other medications. − A consultation with the departments of respiration and infectious diseases. − Subject hospitalization. − Supportive treatment (oxygen inhalation, etc.). − If there is no improvement within 3-5 days, additional tests shall be considered along with an additional immunosuppressive treatment, such as the use of a TNF inhibitor (for example, infliximab

			5mg/kg, once every 2 weeks). Note: It is important to rule out sepsis and refer to the general instructions of infliximab for use. − Once there is improvement, steroids are gradually reduced for ≥ 28 days. In addition, prophylactic use of antibiotics, anti-fungal, and especially anti-PCP agents shall be considered (refer to current NCCN guidelines for the treatment of cancer-related infections (category 2B recommendations))[a].
Diarrhoea/Enterocolitis	All grades	General guidelines	For immune-mediated response of all grades: − Symptoms that may be associated with diarrhoea/enterocolitis (abdominal pain, spasm, or change in bowel habits such as increased bowel frequency or blood stools compared to baseline), or symptoms associated with intestinal perforation (such as sepsis, peritoneal irritation sign, and bowel obstruction) shall be monitored. − Subjects shall be fully evaluated to rule out any other cause (e.g., progressive disease, other medications or infections), including tests for Clostridium difficile toxins. − In order to prevent progression to higher-grade adverse events, steroids shall be considered in the absence of other clear causes, even in the case of low-grade adverse events.

			− Analgesics shall be used with caution; such drugs may mask the symptoms of peritoneal inflammation and perforation.
	Grade 1 (Defecation frequency is increased by <4 times/day compared to baseline)	No administration adjustment is required.	For grade 1: − Symptomatic deterioration shall be closely monitored. − Symptomatic treatment shall be considered, including fluid and electrolyte replacement, dietary changes (e.g., colitis diet recommended by the American Dietetic Association), and loperamide treatment. Probiotics can be used according to the clinical judgment of the attending physician.
	Grade 2 (Defecation frequency is increased by 4-6 times/day compared to baseline)	Suspend the administration of study drug/study protocol until the toxicity is relieved to ≤ grade 1. • If the toxicity is aggravated, treatment is performed according to those suitable for grade 3 or grade 4 responses. • If the toxicity is improved to ≤ grade 1, the study drug/study protocol can be resumed after the dose reduction of steroid is completed.	For grade 2: − Symptomatic treatment shall be considered, including fluid and electrolyte replacement, dietary changes (e.g., colitis diet recommended by the American Dietetic Association), and loperamide and/or budesonide treatment. − Immediately start the treatment with prednisone 1-2 mg/kg/day PO or IV administration of an equivalent dose of other medications. − If there is no improvement or worsening of the AE within 3-5 days after the treatment with prednisone 1-2 mg/kg/day PO or IV administration of an equivalent dose of other medications, the consultation with the department of gastroenterology shall be considered along with further examinations,

			such as an imaging examination and/or colonoscopy, to confirm colitis and exclude the possibility of perforation. In addition, IV administration of 2-4 mg/kg/day methylprednisolone shall be started immediately. − If there is still no improvement within 3-5 days after the treatment with IV administration of 2-4 mg/kg/day methylprednisolone, an immunosuppressive treatment, such as the use of a TNF inhibitor (for example, infliximab 5mg/kg, once every 2 weeks), shall be started immediately. Note: It is important to rule out sepsis and refer to the general instructions of infliximab for use. − If there is still no improvement to ≤ grade 1 in 3-4 days, consult with the physician. − Once there is improvement, steroids are gradually reduced for ≥ 28 days. In addition, prophylactic use of antibiotics, anti-fungal or anti-PCP agents shall be considered (refer to current NCCN guidelines for the treatment of cancer-related infections (category 2B recommendations))[a].
	Grade 3 or 4 (Grade 3: Defecation frequency is increased by ≥7 times/day compared to baseline;	Permanent discontinuation of the study drug/study protocol.	For grade 3 or 4: - Immediately start the empiric treatment with methylprednisolone 2-4 mg/kg/day or IV administration of an equivalent dose of other medications. - The frequency of bowel movements and stool

	Grade 4: Life-threatening consequences)		volume shall be monitored along with sufficient fluid replacement. - When applicable, consult the department of gastroenterology for imaging or/and colonoscopy examinations. If there is still no improvement within 3-5 days after the treatment with IV administration of 2-4 mg/kg/day methylprednisolone or an equivalent dose of other medications, an immunosuppressive treatment (for example, infliximab 5 mg/kg, once every 2 weeks) shall be started immediately. Note: It is important to consult with department of gastroenterology to rule out intestinal perforation and refer to the general instructions of infliximab for use. - Once there is improvement, steroids are gradually reduced for ≥ 28 days. In addition, prophylactic use of antibiotics, anti-fungal or anti-PCP agents shall be considered (refer to current NCCN guidelines for the treatment of cancer-related infections (category 2B recommendations))[a].
Hepatitis (elevated LFT) Infliximab shall not be used to treat immune-related hepatitis.	All grades	General guidelines	For immune-mediated response of all grades: - Monitor and assess liver functions: AST, ALT, ALP, and total bilirubin. - Assess other possible causes (e.g., viral hepatitis, progressive disease, concomitant medication).
	Grade 1	No dose adjustment is required. • If the AE is aggravated, it will be treated as a grade 2 event.	For grade 1: - Continue to monitor the LFT according to the protocol.

	AST or ALT ≥ 3x ULN and/or TB ≥ 1.5x ULN		
	Grade 2 (AST or ALT > 3-5x ULN and/or TB > 1.5-3.0x ULN)	Suspend the administration of study drug/study protocol until grade 2 response is relieved to ≤ grade 1 • If the toxicity is aggravated, treatment is performed according to those suitable for grade 3 or grade 4 responses. • If the toxicity is improved to ≤ grade 1 or baseline, the study drug/study protocol can be resumed after the dose reduction of steroid is completed.	For grade 2: - Regularly and frequently check the level of LFT (for example, every 1-2 days) until the elevated indicator improves or recovers. - If there is still no improvement to ≤ grade 1 in 1-2 days, consult with the physician. - Immediately start the treatment with prednisone 1-2 mg/kg/day PO or IV administration of an equivalent dose of other medications if the event persists (> 3-5 days) or worsens. - If there is still no improvement within 3-5 days after the treatment with 1-2 mg/kg/day prednisone PO or IV administration of an equivalent dose of other medications, additional examination shall be considered along with an immediate treatment with IV administration of 2-4 mg/kg/day of methylprednisolone. - If there is still no improvement within 3-5 days after the treatment with IV administration of 2-4 mg/kg/day methylprednisolone, an immunosuppressant (mycophenolate mofetil) shall be used immediately. If mycophenolate mofetil is not accessible, discuss the issue with the physician. Infliximab shall not be used.

			- Once there is improvement, steroids are gradually reduced for ≥ 28 days. In addition, prophylactic use of antibiotics, anti-fungal or anti-PCP agents shall be considered (refer to current NCCN guidelines for the treatment of cancer-related infections (category 2B recommendations))[a].
	Grade 3 or 4 (Grade 3: AST or ALT > 5-20x ULN and/or TB > 3.0-10x ULN) (Grade 4: AST or ALT > 20x ULN and/or TB > 10x ULN)	For grade 3: If transaminase is increased by ≤ 8x ULN or bilirubin is increased by ≤ 5x ULN: • Suspend the administration of study drug/study protocol until it is relieved to ≤ grade 1 or baseline. • If the elevated indicator is reduced to ≤ grade 1 or baseline within 14 days, the study drug/study protocol is resumed at the next scheduled dose. • If the elevated indicator dose not reduce to ≤ grade 1 or baseline within 14 days, the study drug/study protocol is permanently discontinued. If transaminase is increased by > 8x ULN or bilirubin is increased by > 5x ULN, the study drug/study protocol is discontinued.	For grade 3 or 4: - Immediately start the empiric treatment with methylprednisolone 1-4 mg/kg/day or IV administration of an equivalent dose of other medications. - If there is still no improvement within 3-5 days after the treatment with IV administration of 1-4 mg/kg/day methylprednisolone or an equivalent dose of other medications, an immunosuppressant (mycophenolate mofetil) shall be used immediately. If mycophenolate mofetil is not accessible, discuss the issue with the physician. Infliximab shall not be used. - Consultation with liver specialists, abdominal examination and imaging examination (if applicable) - Once there is improvement, steroids are gradually reduced for ≥ 28 days. In addition, prophylactic use of antibiotics, anti-fungal or anti-PCP agents shall be considered (refer to current NCCN guidelines for the treatment of cancer-related infections (category 2B recommendations))[a].

		For the initial finding that meets the criteria of the Hy's Law (ALT > 3x ULN + bilirubin > 2x ULN) without cholestasis (i.e., increased ALP), if no other cause can be determined, the study drug/study protocol is permanently discontinued. For grade 4: Permanent discontinuation of the study drug/study protocol.	
Nephritis or renal insufficiency (increased serum creatinine)	All grades	General guidelines	For immune-mediated response of all grades: - Consult with nephrology specialists. - Signs and symptoms that may be associated with changes in renal function (e.g., urine routine, increased blood BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decreased urine volume, proteinuria, etc.) shall be monitored. - Subjects shall be fully evaluated to rule out any other possible causes (e.g., progressive disease or infection). - In order to prevent potential progression to higher-grade adverse events, steroids shall be considered in the absence of other clear causes, even in the case of low-grade (grade 2) adverse events.
	Grade 1	No administration adjustment is required.	For grade 1: - Blood creatinine and any accompanying symptoms

	(serum creatinine > 1-1.5x baseline value; > 1-1.5x ULN)		shall be monitored once a week. • If the creatinine level returns to baseline, resume its periodic testing. • If creatinine is abnormally aggravated, it shall be treated as grade 2, grade 3 or grade 4 adverse events depending on its severity. − Symptomatic treatments shall be considered, including fluid and electrolyte replacement, and the use of diuretics.
	Grade 2 (serum creatinine > 1.5-3.0x baseline; > 1.5-3.0x ULN)	Suspend the administration of study drug/study protocol until it is relieved to ≤ grade 1 or baseline. • If the toxicity is aggravated, treatment is performed according to those suitable for grade 3 or grade 4 responses. • If the toxicity is improved to ≤ grade 1 or baseline, the study drug/study protocol can be resumed after the dose reduction of steroid is completed.	For grade 2: − Symptomatic treatments shall be considered, including fluid and electrolyte replacement, and the use of diuretics. − Blood creatinine is carefully monitored once every 2-3 days, as well as when its monitoring is clinically needed. − Consult with nephrology specialists and consider kidney biopsy if there is clinical indication. − Immediately start the treatment with prednisone 1-2 mg/kg/day PO or IV administration of an equivalent dose of other medications if the event persists (> 3-5 days) or worsens. − Within 3-5 days after the treatment with 1-2 mg/kg/day prednisone PO or IV administration of an equivalent dose of other medications, if there is still no improvement or if the event worsens, additional examinations shall be considered along with an

			immediate treatment with IV administration of 2-4 mg/kg/day of methylprednisolone. − Once there is improvement, steroids are gradually reduced for ≥ 28 days. In addition, prophylactic use of antibiotics, anti-fungal or anti-PCP agents shall be considered (refer to current NCCN guidelines for the treatment of cancer-related infections (category 2B recommendations))[a]. − After the event returns to baseline, the study drug/study protocol is resumed along with routine monitoring of serum creatinine carried out according to the study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine > 3.0x baseline; > 3.0-6.0 x ULN; Grade 4: serum creatinine > 6.0x ULN)	Permanent discontinuation of the study drug/study protocol.	For grade 3 or 4: − Level of serum creatinine is closely monitored daily. − Consult with nephrology specialists and consider kidney biopsy if there is clinical indication. − Immediately start the treatment with prednisone 1-2 mg/kg/day PO or IV administration of an equivalent dose of other medications. − Within 3-5 days after the treatment with 1-2 mg/kg/day prednisone PO or IV administration of an equivalent dose of other medications, if there is still no improvement or if the event worsens, additional examinations shall be considered along with an immediate treatment with IV administration of 2-4 mg/kg/day of methylprednisolone.

			− Once there is improvement, steroids are gradually reduced for ≥ 28 days. In addition, prophylactic use of antibiotics, anti-fungal or anti-PCP agents shall be considered (refer to current NCCN guidelines for the treatment of cancer-related infections (category 2B recommendations))[a].
Rash (Except for skin bulla)	All grades (For definitions of severity/grade, refer to NCI CTCAE Version 4.03, based on the type of rash)	General guidelines	For immune-mediated response of all grades: − Signs and symptoms of dermatitis (rash and pruritus) shall be monitored. − ** If any skin bulla forms, contact the physician and discontinue the study drug**.
	Grade 1	No administration adjustment is required.	For grade 1: − Consider symptomatic treatments, including oral anti-pruritic drugs (e.g., diphenhydramine or hydroxyzine) and topical treatments (e.g., urea cream).
	Grade 2	For a sustained (> 1-2 weeks) grade 2 event, suspend the administration of study drug/study protocol until it is relieved to ≤ grade 1 or baseline. • If the toxicity is aggravated, treatment is performed according to those suitable for grade 3 responses. • If the toxicity is improved to ≤ grade 1 or baseline, the study drug/study protocol can be resumed	For grade 2: − Consult with dermatologists. − Consider symptomatic treatments, including oral anti-pruritic drugs (e.g., diphenhydramine or hydroxyzine) and topical treatments (e.g., urea cream). − Consider taking moderate-strength topical steroid treatment. − Within 3-5 days after the symptomatic treatment and/or the use of a moderate-strength topical steroids,

		after the dose reduction of steroid is completed.	if there is still no improvement or if the event worsens, discuss with the physician and immediately start the systemic steroid treatment (prednisone 1-2 mg/kg/day PO or IV administration of an equivalent dose of other medications) if the event persists (>3-5 days) or worsens. − If the AE persists for > 1-2 weeks or recurs, consider a skin biopsy.
	Grade 3 or 4	For grade 3: Suspend the administration of study drug/study protocol until it is relieved to ≤ grade 1 or baseline. If the grade 3 rash cannot be improved to ≤ grade 1 or baseline within 30 days after the study drug/study protocol is suspended, the study drug/study protocol shall be permanently discontinued. For grade 4: Permanent discontinuation of the study drug/study protocol.	For grade 3 or 4: − Consult with dermatologists. − Immediately start the empiric treatment with 1-4 mg/kg/day methylprednisolone or IV administration of an equivalent dose of other medications. − Hospitalization is considered. − Monitor the extent of the rash (rule of nine)]. − If clinically feasible, consider a skin biopsy (preferably more than 1 site is examined). − Once there is improvement, steroids are gradually reduced for ≥ 28 days. In addition, prophylactic use of antibiotics, anti-fungal or anti-PCP agents shall be considered (refer to current NCCN guidelines for the treatment of cancer-related infections (category 2B recommendations))[a]. − Discuss with the physician.
Endocrine disorders (hyperthyroidism, hypothyroidism,	All grades (For definitions of CTC grade/severity	General guidelines	For immune-mediated response of all grades: − Consult with endocrinologists.

hypopituitarism, adrenal insufficiency, etc.)	based on the type of endocrine disorders, refer to NCI CTCAE Version 4.03)		− Subjects are monitored for signs and symptoms of endocrine disorders. Non-specific symptoms include headache, fatigue, behavioral changes, mental state changes, vertigo, abdominal pain, abnormal bowel habit, hypotension, and weakness. − Subjects shall be fully evaluated to rule out any other possible causes (e.g., progressive disease including brain metastases or infection). − Monitoring and evaluation of thyroid functions: TSH, free T3 and free T4 and other relevant endocrine laboratory tests based on the suspected endocrine disease. − If a subject's AE is considered to be caused by autoimmune factors (e.g., thyroiditis, pancreatitis, pituitary inflammation, diabetes insipidus), the investigator shall send a blood sample for the test of corresponding autoimmune antibodies.
	Grade 1	No administration adjustment is required.	For grade 1 (including asymptomatic TSH elevation): − Appropriate endocrine function tests are performed to monitor subjects. − If TSH < 0.5x LLN or TSH > 2x ULN, or if TSH is outside its normal range in two consecutive measurements, free T4 shall be monitored in the following cycles according to clinical indications. In addition, consultation with department of endocrinology shall be considered.

	Grade 2	In addition to hypothyroidism, the administration of study drug/study protocol shall be suspended for grade 2 endocrine disorders until the patient becomes clinically stable. • If the toxicity is aggravated, treatment is performed according to those suitable for grade 3 or grade 4 responses. Once the dose of steroids is gradually reduced and the event is stabilized, the study drug/study protocol can be resumed. For subjects with endocrine disorders who may require long-term or sustained steroid replacement therapy, they may resume the treatment of the study drug/study protocol under the following conditions: 1. The event has become stabilized and controlled. 2. The patient is clinically stable according to the judgment of the investigator or attending physician.	For grade 2 (including symptomatic endocrine disorders): − Simple hypothyroidism can be treated with a replacement therapy without treatment interruption and without a corticosteroid treatment. − Hormone replacement therapy can be initiated according to the needs of clinical demands. − Endocrine functions are assessed. In addition, pituitary scans can be considered based on clinical indications. − For subjects with abnormal results of endocrine examinations other than subjects with simple hypothyroidism, short-term corticosteroids shall be considered (e.g., 1-2 mg/kg/day methylprednisolone or IV administration of an equivalent dose of other medications) along with an immediate replacement therapy using related hormones (e.g., levothyroxine, hydrocortisone, or sex hormones). − Once there is improvement, steroids are gradually reduced for ≥ 28 days. In addition, prophylactic use of antibiotics, anti-fungal or anti-PCP agents shall be considered (refer to current NCCN guidelines for the treatment of cancer-related infections (category 2B recommendations))[a]. − For subjects with normal results of endocrine examinations (laboratory or MRI results), laboratory

		1. The dose of prednisone or an equivalent dose of other medications is ≤ 10 mg/day.	tests/MRI scans shall be repeated according to clinical indications.
	Grade 3 or 4	For grade 3 or 4 endocrine disorders (except for hypothyroidism), suspend the administration of study drug/study protocol until the symptoms of endocrine disorders are under control. Once the dose of steroids is gradually reduced and the event is stabilized, the study drug/study protocol can be resumed.	For grade 3 or 4: − Consult with endocrinologists. − Simple hypothyroidism can be treated with a replacement therapy without treatment interruption and without a corticosteroid treatment. − Immediately start the empiric treatment with methylprednisolone 1-2 mg/kg/day or IV administration of an equivalent dose of other medications. − Hormone replacement therapy can be initiated if needed. − For adrenal crisis, severe dehydration, hypotension or shock: Immediately start the intravenous injection of corticosteroids with mineralocorticoid activity. − Once there is improvement, steroids are gradually reduced for ≥ 28 days. In addition, prophylactic use of antibiotics, anti-fungal or anti-PCP agents shall be considered (refer to current NCCN guidelines for the treatment of cancer-related infections (category 2B recommendations))[a]. − Discuss with the physician.
Neurotoxicity (Including but not limited to marginal	All grades (For definitions of CTC grade/severity	General guidelines	For immune-mediated response of all grades:

encephalitis and autonomic neuropathy, excluding myasthenia gravis and Guillain-Barre syndrome)	based on the grading of neurotoxicity, refer to NCI CTCAE Version 4.03)		− Subjects shall be fully evaluated to rule out any other possible causes (e.g., progressive disease, infection, metabolic syndrome, or drug treatment). − The systemic symptoms of the subjects shall be monitored (headache, nausea, vertigo, behavioral changes, or weakness). − Appropriate diagnostic tests shall be considered (e.g., electromyography and nerve conduction tests). − If appropriate, conduct a consultation with the department of neurology and carry out a symptomatic treatment.
	Grade 1	No administration adjustment is required.	For grade 1: − See the recommendation for "all grades" shown above.
	Grade 2	For acute motor neuropathy or neurotoxicity, suspend the administration of study drug/study protocol until the event is relieved to ≤ grade 1. For sensory neuropathy/neuropathic pain, consider to suspend the administration of study drug/study protocol until the event is relieved to ≤ grade 1. • If the toxicity is aggravated, treatment is performed according to	For grade 2: − Discuss with the physician. − Consultation with the department of neurology. − Sensory neuropathy/neuropathic pain can be treated with a suitable drug (e.g., gabapentin or duloxetine). − Immediately start the treatment with systemic steroids (prednisone 1-2 mg/kg/day PO or IV administration of an equivalent dose of other medications). − If there is still no improvement within 3-5 days after the treatment with 1-2 mg/kg/day prednisone PO or IV administration of an equivalent dose of other medications, additional examination shall be

		those suitable for grade 3 or grade 4 responses. Once the dose of steroids is gradually reduced and the event is stabilized to ≤ grade 1, the study drug/study protocol can be resumed.	considered along with an immediate treatment with other immunosuppressive treatment (such as IVIG).
	Grade 3 or 4	For grade 3: Suspend the administration of study drug/study protocol until it is relieved to ≤ grade 1. If the grade 3 irAE has not been alleviated to ≤ grade 1 within 30 days, the dosing of the study drug/study protocol shall be permanently discontinued. For grade 4: Permanent discontinuation of the study drug/study protocol.	For grade 3 or 4: − Discuss with the physician. − Consultation with the department of neurology. − Hospitalization is considered. − Immediately start the empiric treatment with methylprednisolone 1-2 mg/kg/day or IV administration of an equivalent dose of other medications. − If there is still no improvement within 3-5 days after the IV administration of corticosteroids, additional examinations shall be considered along with an immediate treatment with other immunosuppressive treatment (such as IVIG). − Once the event becomes stable, gradually reduce the steroid dose for ≥ 28 days.
Peripheral Motor Syndrome (such as Guillain-Barre syndrome and myasthenia gravis)	All grades	General guidelines	For immune-mediated response of all grades: − The timely diagnosis of immune-mediated peripheral motor syndrome is important because some subjects may experience unanticipated acute decompensation, leading to possible disability or, in the worst case, death. Special attention shall be paid to certain

			precursor symptoms that may indicate serious consequences, such as significant dysphagia, rapid progression of weakness, respiratory insufficiency, or signs of autonomic disorders. – Subjects shall be fully evaluated to rule out any other possible causes (e.g., progressive disease, infection, metabolic syndrome, or drug treatment). It shall be noted that the diagnosis of immune-mediated peripheral motor syndrome is particularly challenging in subjects with cancer due to the multiple confusing effects exerted by cancer (and its treatment) on the nerve axis. Given the importance of timely and accurate diagnosis, it is crucial to lower the threshold for neurology consultation. – If such a condition is suspected, a neurophysiological diagnosis shall be performed (e.g., if muscle weakness is suspected, EMG and nerve conduction tests as well as “repetitive stimulation” can be performed), and it is best to assist the examination via a neurology consultation. – It is important to consider that the use of steroids as the primary treatment for Guillain-Barre syndrome is generally ineffective. For subjects in need of treatment, an IVIG treatment shall be initiated, followed by a plasma treatment if the IVIG therapy is ineffective.

	Grade 1	No administration adjustment is required.	For grade 1: − Discuss with the physician. − Special attention shall be paid to certain precursor symptoms that may indicate serious consequences (such as those mentioned above). − Neurology consultation is required unless the symptoms are extremely mild and stable.
	Grade 2	Suspend the administration of study drug/study protocol until it is relieved to ≤ grade 1. If the event has not been alleviated to ≤ grade 1 within 30 days, or if there are signs of respiratory insufficiency or autonomic disorders, the dosing of the study drug/study protocol shall be permanently discontinued.	For grade 2: − Discuss with the physician. − Special attention shall be paid to certain precursor symptoms that may indicate serious consequences (such as those mentioned above). − Consultation with the department of neurology. − Sensory neuropathy/neuropathic pain can be treated with a suitable drug (e.g., gabapentin or duloxetine). Myasthenia gravis: o Steroids can be used to successfully treat myasthenia gravis. It is important to consider that a steroid treatment (especially at high doses) may lead to a transient exacerbation of muscle weakness, so the administration of steroids shall be monitored under the guidance of a neurologist. o Subjects who are unable to tolerate steroids may be considered for a plasma exchange or IVIG treatment. Given the unique needs of

			each patient, it is best to consult a neurologist when the decision is made. o In the presence of myasthenia gravis-like neurotoxicity, a treatment using acetylcholinesterase (AChE) inhibitors can be considered in addition to steroids. If the treatment is successful, it can also help with the diagnosis. Guillain-Barre syndrome: o It is important to recognize that steroids are generally not considered as the main effective treatment for Guillain-Barre syndrome. o For subjects in need of treatment, an IVIG treatment shall be initiated first, followed by plasma exchange if the IVIG treatment is ineffective.
	Grade 3 or 4	For grade 3: Suspend the administration of study drug/study protocol until it is relieved to ≤ grade 1. If the event has not been alleviated to ≤ grade 1 within 30 days, or if there are signs of respiratory insufficiency or autonomic disorders, the dosing of the study drug/study protocol shall be permanently discontinued.	For grade 3 or 4 (severe or life-threatening events): − Discuss with the physician. − Hospitalization is recommended. − The symptoms shall be monitored along with a consultation with the department of neurology. Myasthenia gravis: o Steroids can be used to successfully treat myasthenia gravis. The administration of steroid shall be monitored under the guidance of a neurologist.

		For grade 4: Permanent discontinuation of the study drug/study protocol.	o Subjects who are unable to tolerate steroids may be considered for a plasma exchange or IVIG treatment. o In the presence of myasthenia gravis-like neurotoxicity, a treatment using AChE inhibitors can be considered in addition to steroids. If the treatment is successful, it can also help with the diagnosis. Guillain-Barre syndrome: o It is important to recognize that steroids are generally not considered as the main effective treatment for Guillain-Barre syndrome. o For subjects in need of treatment, an IVIG treatment shall be initiated first, followed by plasma exchange if the IVIG treatment is ineffective.

Appendix 9: Prohibited Traditional Chinese Medicines

Prohibited Traditional Chinese Medicines

Hua Zheng Hui Sheng Tablet	Anticancer Ping Pill
Brucea Javanica Oil Soft Capsule/Brucea Javanica Oil Injection	Fu Kang Capsule
Zhe Mu Syrup	Xiao Ai Ping
Cantharidin/Cantharidin Injection/Cantharidin Capsule	Ping Xiao Capsule
Hua Chan Su	Ping Xiao Tablet
Toad Venom	Shen Dan San Jie Capsule
Kang Ai Injection	An Kang Xin Capsule
Kang Lai Te	Bo Sheng Ai Ning
Herba Sarcandrae Injection	Zedoary Turmeric Oil Glucose Injection
Ai Di Injection	Kang Li Xin Capsule
A Wei Hua Pi Cream	Ci Dan Capsule
Shenmai	Lightyellow Sophora Root
Placental Polypeptide	

Note: Traditional Chinese medicines prohibited during the trial include but not limited to the above drugs.

Title Page

Protocol Title: A Randomized, Double-Blind, Multicenter, Phase III Study to Compare Clinical Efficacy and Safety of HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin-Etoposide) in Previously Untreated Patients with Extensive Stage Small Cell Lung Cancer (ES-SCLC)

Protocol Number: HLX10-005-SCLC301

Amendment Number: Not applicable

Compound Number: HLX10

Short Title: A Randomized, Double-blind, Placebo-Controlled Phase III Study to Investigate Efficacy and Safety of HLX10 + Chemotherapy (Carboplatin- Etoposide) in Patients with Extensive Stage Small Cell Lung Cancer (ES-SCLC)

Sponsor Name and Legal Registered Address: Shanghai Henlius Biotech, Inc. Room 303 & 304, Block 7, No. 1999, Zhangheng Road, China (Shanghai) Pilot Free Trade Zone.

Regulatory Agency Identifying Number(s): NMPA Approval Document Number: 2018L02201, EudraCT Number: 2019-003063-21

Approval Date: 05 February 2021

Investigator Agreement Page

Declaration of the Global Coordinating Investigator

Title: A Randomized, Double-Blind, Multicenter, Phase III Study to Compare Clinical Efficacy and Safety of HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin-Etoposide) in Previously Untreated Patients with Extensive Stage Small Cell Lung Cancer (ES-SCLC)

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the guidelines on Good Clinical Practice.

Global Coordinating Investigator

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

Investigator Agreement Page

Declaration of the Principal Investigator

Title: A Randomized, Double-Blind, Multicenter, Phase III Study to Compare Clinical Efficacy and Safety of HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin-Etoposide) in Previously Untreated Patients with Extensive Stage Small Cell Lung Cancer (ES-SCLC)

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the guidelines on Good Clinical Practice.

Principal Investigator

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Signature Date

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Name (block letters)

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Title (block letters)

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Institution (block letters)

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Phone number

Sponsor Signatory

Wenying Kang, Medical Director of Global Clinical Medical Affairs Shanghai Henlius Biotech, Inc.	**Date**

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY		
Version	**Date**	**Notes**
Version 4.0	05 February 2021	This document Global level
Version 3.0	08 April 2020	This document
Version 2.0	27 Sep 2019	Global Level
Version 1.0	04 Mar 2019	Applicable for China only

Overall Rationale for the Amendment 3:

Protocol version 3.0 was updated to Version 4.0, based on comments from the European Medicines Agency as part of a Scientific Advice procedure, comments from the Bulgarian Drug Agency, and from the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (Poland Regulatory Agency), additional clarifications, and correction of minor inconsistencies between sections. In addition, minor corrections, including typographical/grammatical errors, have been made. Changes made during development of Version 4.0 are clarified as follows:

Section # and Name	**Description of Change(s)** (*new text is in bold and underlined, deleted text is struck-through)*	**Brief Rationale**
1.1 Synopsis 3 Objectives and Endpoints 8.3 Study Assessments 9.4.1.2 Analysis of secondary efficacy endpoints	Section 1.1 **PFS2 (assessed by the investigator based on RECIST 1.1)** Section 3 **PFS2 (assessed by the investigator based on RECIST 1.1)** Section 8.3 **Progression-free survival 2 (PFS2) is defined as time from randomization to second/subsequent objective tumor progression on next-line treatment or death from any cause.** Section 9.4.1.2 **Progression-free survival 2 (assessed by the investigator based on RECIST 1.1). PFS2 is defined as time from randomization to second/subsequent objective tumor progression on next-line treatment or death from any cause. It will be analyzed using the same method as that for PFS.**	Revision based on comments from the European Medicines Agency
1.3 Schedule of Activities (SoA)	Section 1.3 Schedule of activities table footnote #12 (initial treatment period and	Removal of myoglobin testing. It is recommended

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
8.1 Tests and Evaluations during the Study	post-PD treatment period): …myocardial **<u>function</u>** detection includes troponin-I **<u>(TnI)</u>**/ ~~or~~ troponin-T **<u>(TnT)</u>**, creatine kinase isoenzyme (CK-MB)/**<u>creatine kinase (CK), and Brain Natriuretic Peptide (BNP)/N-terminal pro-Brain Natriuretic Peptide (NT-pro BNP)</u>**~~and myoglobin~~; Section 8.1, Table 5 Myocardial **<u>function</u>**: Troponin-I **<u>(TnI)</u>**/~~or~~ **<u>Troponin-T (TnT)</u>**, Creatine kinase isoenzyme (CK-MB**<u>)/creatine kinase</u>** (CK), **<u>myoglobin Brain Natriuretic Peptide (BNP)/N-terminal pro-Brain Natriuretic Peptide (NT-pro BNP)</u>**~~, Myoglobin~~ Footnote:-**Routine blood test, blood chemistry, coagulation function, **myocardial <u>function</u>** and urinalysis	that the biomarker used for diagnosis of acute myocardial infarction is cardiac troponin due to its sensitivity and accuracy. Myoglobin remains a biomarker of secondary relevance as compared to troponin-assessments, hence it was removed.
1.3 Schedule of Activities (SoA) 5.2 Exclusion Criteria 8.1 Tests and Evaluations during the study 8.2.1 Screening Period (day -28 to day -1)	Section 1.3 Schedule of activities table: **<u>Tuberculosis screening</u>** Footnote#15 (initial treatment period) Section 5.2 Active **<u>or latent</u>** pulmonary tuberculosis. Section 8.1 and Table 5 Local laboratory tests performed at study sites include routine blood test, serum biochemistry, coagulation, myocardial enzymogram, urinalysis, thyroid function, virology, **<u>tuberculosis screening (as requested by the Bulgarian Drug Agency for Bulgarian subjects)</u>** and pregnancy test. Section 8.2.1 Local laboratory tests: routine blood test, serum biochemistry, coagulation, myocardial enzymogram, urinalysis, thyroid function,	Addition of tuberculosis testing at Screening and addition of latent tuberculosis in exclusion criteria as requested by the Bulgarian Drug Agency for Bulgarian subjects

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	pregnancy test (for females of childbearing age only)**,** ~~and~~ virology **and tuberculosis screening (as requested by the Bulgarian Drug Agency for Bulgarian subjects)**.	
2.3.2 Identified and potential risks	In the phase II study of HLX10 in patients with previously treated HCC, 1 subject received HLX10 (3 mg/kg) combined with HLX04 (5 mg/kg) once every 2 weeks experienced DLT at safety run in stage (increased total bilirubin is 39.4 ~~m~~**μ**mol/L which is >2 mg/dL and considered to be caused by hepatocellular cancer progression)	Correction of typographical error for total bilirubin unit
Sponsor Signatory	~~Xin Zhang~~**Wenying Kang** ~~Vice president~~ **Medical Director** of Global Clinical Medical Affairs	To update the Sponsor signatory information.
1.3 Schedule of Activities (SoA) 1.1 Synopsis 3 Objectives and Endpoints 8.1 Tests and Evaluations during the Study 8.2.2 Treatment Period 8.4 Safety Assessment	Section 1.3 Footnote 4# (Initial Treatment Period) ECOG performance status, serum pregnancy test, blood routine, biochemistry, coagulation, **myocardial function,** urinalysis and thyroid function (T3 or FT3, T4 or FT4, TSH) should be completed within 7 days before randomization, and the subjects should meet the corresponding inclusion/exclusion criteria for enrollment. Section 1.1 and Section 3: Safety Endpoints • Adverse events (AEs) (including serious adverse events [SAEs]), laboratory tests (routine blood test, blood chemistry, coagulation function, urinalysis, **myocardial function and** thyroid function), 12-lead electrocardiogram (12-lead ECG), vital signs, and physical examination, etc. Section 8.1 Table 5	Add “myocardial function” in laboratory tests to be consistent with Table 5.

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	Routine blood test, blood chemistry, coagulation function**, myocardial function** and urinalysis must be performed at screening and within 3 days prior to drug administration every treatment cycle. Section 8.2.2 (Initial treatment visit and Post-PD treatment visit) Routine blood test, biochemistry, coagulation**, myocardial function** and urinalysis should be performed within 3 days pre-dose in each treatment cycle; for combined chemotherapy, routine blood tests should be performed on Day 8 (± 3 days) of each treatment cycle. Section 8.4 Safety assessments variables include AEs (including SAEs), laboratory tests (routine blood test, blood chemistry test, coagulation test, routine urine test, **myocardial function** and thyroid function test), 12-lead ECG, vital signs, and physical examination.	
1.3 Schedule of Activities (SoA) 8.1 Tests and Evaluations during the Study 8.2.2. Treatment Period	Section 1.3 Footnote 16# (Initial Treatment Period and Post-PD Treatment Period) Computerized tomography (CT) or magnetic resonance imaging (MRI) should be performed at screening, every 6 weeks (± 7 days) during the first 48 weeks after the start of study treatment, and every 9 weeks (± 7 days) after week 48 on sites including brain, chest, abdomen, pelvic cavity and any other sites suspected to have tumor lesions, in which brain MRI or CT (preferably MRI) and bone scans are required for all subjects at screening, and are performed in the treatment period as determined by the investigator according to clinical needs **(if baseline brain CT/MRI shows that brain metastasis is not present, the subject should have follow up brain imaging only if clinically indicated at the discretion of the investigator. If baseline brain CT/MRI has confirmed central nervous system (CNS) metastasis, continuous brain imaging test should be carried out as part of the**	Revision based on NTF clarification.

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	regular RECIST evaluation assessments); examination methods at the same site should be consistent as much as possible throughout the study; if there are no contraindications, contrast agent should be used. The investigator and IRRC respectively assess the tumor images according to RECIST 1.1 (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation. If tumor assessment has been performed within 28 days prior to the first dose by the same methods and devices in the same hospital, it may serve as the baseline tumor assessment. At the EOT visit, if tumor imaging has been performed within the last 4 weeks, a re-test is not required. For subjects who discontinued for reasons other than disease progression, radiological assessments are to be continued as scheduled, until disease progression, initiation of new antineoplastic therapy, withdrawal of ICF, death, or **end of study**~~EOT~~, whichever occurs first. Section 8.1 Subjects should undergo CT or MRI (including brain, chest, abdomen, pelvic cavity and any other sites suspected of having tumor lesions) at screening (within 4 weeks pre-dose), every 6 weeks (± 7 days) during the first 48 weeks after the start of study treatment, and every 9 weeks (± 7 days) after week 48 **(if baseline brain CT/MRI shows that brain metastasis is not present, the subject should have follow up brain imaging only if clinically indicated at the discretion of the investigator. If baseline brain CT/MRI has confirmed CNS metastasis, continuous brain imaging test should be carried out as part of the regular RECIST evaluation assessments)**. Section 8.2.2	

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	Initial treatment visit and Post-PD treatment visit (Optional) **(if the baseline brain CT/MRI shows that brain metastasis is not present, the subject should have follow-up brain imaging only if clinically indicated at the discretion of the investigator. If the baseline brain CT/MRI confirms CNS metastasis, a continuous brain imaging test should be carried out as part of the regular RECIST evaluation assessments);**	
2.1 Background	**Anti-PD-1 monoclonal antibodies have been approved for melanoma, non-small cell lung cancer (NSCLC), SCLC, head and neck squamous cell cancer, urothelial carcinoma, microsatellite instability-high or mismatch repair deficient solid tumors and colorectal cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma (HCC), Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, bladder cancer, primary mediastinal large B-cell lymphoma and classical Hodgkin's lymphoma. Numerous clinical studies are ongoing with anti-PD-1 antibodies, either as monotherapy or in combination with various agents.**	Add the approved indication of anti-PD-1 antibodies in background.
2.2 Study Rationale	~~Based on the results of the HLX10 preclinical and phase I clinical trials, the currently available pharmacokinetic (PK) and anti-drug antibody (ADA) data support an average body weight dose of HLX10 of 4.5 mg/kg administered every 21 days as the recommended dose for phase III clinical studies.~~ **The available clinical data demonstrated that HLX10 is safe and tolerable in the phase I, first-in-human study in patients with advanced solid tumors, and in other clinical studies in patients with malignant solid tumors. And preliminary efficacy has been observed in some patients with advanced solid tumors in the**	Add available clinical studies information to support the study rationale.

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	first-in-human phase I clinical study (HLX10-001). The safety and efficacy of HLX10 will be further evaluated in clinical studies.	
2.2 Study Rationale	Based on the results of preclinical and clinical studies, Shanghai Henlius Biotech, Inc. planned to conduct a phase III clinical study in previously untreated patients with ES-SCLC worldwide to compare the clinical efficacy **and safety** of HLX10 (recombinant anti-PD-1 humanized monoclonal antibody injection) in combination with chemotherapy (Carboplatin Etoposide).	Correcting a minor typo noted to ensure consistency and was updated in POL PA V2.1.
2.2.1 Preclinical Studies of HLX10	In the dose-finding trial (P16-106-TS), pharmacokinetic **(PK)** test (P16-106-YD), and long-term toxicity test (P16-106-CD) in *cynomolgus* monkeys; receptor occupancy (RO) at different time points was also investigated before and after intravenous injection of different doses of HLX10 to provide a basis for selection of the clinical effective dose and the initial dose.	Correcting a minor typo noted after PA V3.0 was finalized.
2.2.1 Preclinical Studies of HLX10	**Genetic Toxicology Studies** **The genotoxicity isn't required to be evaluated for monoclonal antibodies like HLX10 according to ICHS6 (R1).** ~~No genotoxicity study of HLX10 has been conducted.~~	Re-organized to clarify the genetic toxicology studies information.
2.2.1 Preclinical Studies of HLX10	Tissue cross-reactivity of HLX10 The results of tissue cross-reactivity test of HLX10 in **frozen normal** human showed that HLX10-Biotin (2.0 μg/mL and 0.5 μg/mL) specifically binds to normal human lymphocytes **from** ~~including~~ **the** lymph node~~s~~, ~~the~~ lung~~s~~, ileum, stomach, spleen, fallopian tube~~s~~, colon and thymus ~~tissues~~.	Minor update to wording for tissue cross-reactivity study
2.2.2 Clinical Study of HLX10	~~A clinical study of HLX10 had been approved by US FDA, Taiwan Food and Drug Administration (TFDA) and China NMPA.~~	The most up-to-date clinical studies are added in this protocol.

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	~~Phase I clinical trial of HLX10: A prospective, open-label, dose-escalation study of HLX10 in patients with metastatic or recurrent solid tumors who had failed standard therapy. Bayesian optimal interval design (BOIN) was used to determine the maximum tolerated dose (MTD) of HLX10. The objective of this study was to evaluate the safety, PK characteristics, biomarkers, PD markers, immunogenicity and preliminary efficacy of the study drug. Eligible subjects who meet the inclusion criteria in the screening period will receive infusion of HLX10 at a dose level specified in the protocol once every 2 weeks until disease progression, or up to one year, withdrawal from study, or death, whichever occurs first. Each treatment cycle consists of two doses of study drug, once every 2 weeks. The trial is currently ongoing. The enrollment of patients into the 0.3, 1, and 3 mg/kg groups has been completed, and the safety evaluation is ongoing.~~ **To date, HLX10 has been administered to human subjects in 14 ongoing clinical studies. Clinical studies of HLX10, given as monotherapy or in combination with chemotherapy or other antibodies (anti-VEGF antibody HLX04), are being conducted in patients with advanced solid tumors, previously untreated metastatic non-squamous NSCLC, previously treated unresectable or metastatic MSI-high or mismatch repair deficiency solid tumors, previously treated advanced HCC, gastric cancer, metastatic esophageal squamous cell carcinoma (ESCC), metastatic colorectal cancer (mCRC), relapsed and/or advanced cervical cancer, and advanced head and neck cancer.** **The clinical efficacy and safety results from these studies, as well as the nonclinical toxicology and safety data, provide evidence to support continued clinical development for HLX10.**	

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2.3.1 Potential Benefits	~~Atezolizumab (trade name Tecentriq®), a PD-L1 inhibitor developed by Roche in September 2018, has achieved landmark results in the first-line treatment of SCLC:~~ ~~IMpower 133, a randomized, controlled phase III study evaluating atezolizumab plus carboplatin-etoposide versus placebo plus carboplatin-etoposide in the treatment of untreated extensive SCLC, enrolled 403 patients and randomized at 1:1 with a median follow-up of 13.9 months. Median overall survival was 12.3 months (95% confidence interval [CI], 10.8-15.9) in the atezolizumab plus chemotherapy group and 10.3 months (95% CI, 9.3-11.3) in the placebo plus chemotherapy group (HR = 0.70, 95% CI 0.54-0.91, P = 0.007). Median progression-free survival was 5.2 months (95% CI, 4.4-5.6) in the atezolizumab plus chemotherapy group and 4.3 months (95% CI, 4.2-4.5) in the placebo plus chemotherapy group (HR = 0.77, 95% CI 0.62-0.96, P = 0.02). At the same time, in terms of safety, the safety of Atezolizumab plus chemotherapy was consistent with that in the previous reports and no new toxicity was found.~~ ~~Based on the above study results, Henlius plans to study the anti-tumor activity of HLX10 plus chemotherapy as first-line treatment of ES-SCLC. The preliminary efficacy, safety and tolerability data of PD-L1 plus chemotherapy in the IMpower 133 study supports the use of this treatment in ES-SCLC. The primary objective of this phase III study is to determine the clinical efficacy and safety of HLX10 plus chemotherapy in previously untreated ES-SCLC patients.~~ **Available clinical data for HLX10 include that collected from clinical studies of HLX10, which was given as monotherapy and/or in combination with chemotherapy or other antibody (anti-VEGF antibody HLX04), in patients with advanced solid tumors, previously untreated metastatic non-squamous NSCLC, previously treated unresectable or metastatic MSI-H or dMMR solid tumors,**	The study results of atezolizumab (IMpower 133) in this protocol will be replaced by the interim analysis results of phase I first-in-human study (HLX10-001).

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	previously treated advanced HCC, gastric cancer, metastatic ESCC, mCRC, relapsed and/or advanced cervical cancer, and advanced head and neck cancer. **The available clinical data shows that HLX10 monotherapy or combined with other therapies was safe and tolerable in patients with malignant tumors.** **Only 1 subject in the 3 mg/kg dose cohort (n=6) experienced DLT during the first cycle in the HLX10 first-in-human phase I study in patients with advanced solid tumors with four dose levels (0.3, 1, 3 and 10 mg/kg). The maximum tolerated dose (MTD) was not reached until 10 mg/kg of HLX10 was given every two weeks. Accumulation of HLX10 was observed following multiple dose administration. The 0.3 mg/kg of HLX10 was enough to saturate the PD-1 binding and induce the functional blockade. The efficacy results demonstrated anti-tumor activity of HLX10 in this first-in-human phase I study with DCR of 68.8%, ORR of 6.3%, and median PFS of 107.0 days.** **In the phase II study of HLX10 in patients with previously treated HCC, 1 subject in the dose level A (n=7) of safety run-in stage experienced DLT (increased total bilirubin is 39.4 μmol/L which is >2 mg/dL and considered to be caused by hepatocellular cancer progression).** **The study showed the anti-tumor activity of HLX10 and patients with advanced solid tumors can benefit from HLX10.**	
2.3.2 Identified and Potential Risks	~~The safety evaluation of IMpower 133 in ES-SCLC also showed that the occurrences of AEs in the atezolizumab + EC group and placebo + EC group were comparable, with the occurrences of AEs of any grade being 100% and 96.4% in the two groups, respectively; the occurrences of grade 3-4 AEs were 67.2% and 63.8% in the two groups, respectively. The occurrences of treatment-related AEs were 94.9% and~~	The safety information of atezolizumab (IMpower 133) in this protocol will be replaced by the up-to-date risk information

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	~~92.3%, respectively. The occurrences of SAEs were 37.4% and 34.7%, respectively; the occurrences of immune-related AEs were 39.9% and 24.5%, respectively. The comparisons for occurrences of most common grade 3-4 AEs: Neutropenia (22.7% and 24.5%), anemia (14.1% and 12.2%), neutrophil count decrease (14.1% and 16.8%), thrombocytopenia (10.1% and 7.7%), leukopenia (5.1% and 4.1%). The occurrences of immune-related grade 3-4 AEs in the atezolizumab + EP group were 2% for rash, 1.5% for hepatitis, 2% for infusion-related reactions, and 0.5% for pneumonia.~~ **HLX10 is currently being studied with limited safety information available. The available clinical data from the first-in-human phase I clinical study, shows that the most frequently reported study drug related adverse events were nausea, fatigue and decreased appetite, constipation, vomiting and pyrexia. The severity was mainly grade 1-2. The most frequently reported serious adverse event (SAE) that was greater or equal than grade 3 was pyrexia.** **In another phase I clinical study (HLX10HLX04-001) of the study drug combined with another antibody, no DLT was observed in the 18 subjects when the study drug was administered from 1 mg/kg to 10 mg/kg.** **In the phase II study (HLX10-008-HCC201) of HLX10 in patients with previously treated HCC, 1 subject received HLX10 (3 mg/kg) combined with HLX04 (5 mg/kg) once every 2 weeks experienced DLT at safety run in stage (increased total bilirubin is 39.4 μmol/L which is >2 mg/dL and considered to be caused by hepatocellular cancer progression).** **In the ongoing phase III study (HLX10-002-NSCLC301) of HLX10 in patients with previously untreated non-squamous non-small cell lung cancer (NSCLC), 6 subjects have received HLX10 (4.5 mg/kg) + HLX04 (15 mg/kg) + carboplatin (AUC=5) + pemetrexed**	reported in the Investigator's Brochure.

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	(500 mg/m^2) once every 3 weeks with no major safety concerns. No grade ≥4 hematologic toxicity and grade ≥3 non-hematologic toxicity-safety events and grade ≥2 pneumonia (and no recovery to grade 1 in 3 days) occurred after the treatment of the first cycles. **No serious adverse drug reactions (ADRs) were observed in the first stage of the study (safety run-in period). The most common ADRs included platelet count decreased, white blood cell count decreased, neutrophil count decreased and hypertriglyceridaemia.** **Several other phase II and III clinical studies of the study drug are ongoing, where HLX10 has been administered as monotherapy and/or in combination with chemotherapy or other antibody, in patients with advanced solid tumors, previously untreated metastatic non-squamous non-small cell lung cancer and previously treated unresectable or metastatic MSI-H (microsatellite instability-high) or dMMR (deficiency in mismatch repair) solid tumors. The available clinical data showed that the study drug given as a monotherapy or combined with other therapies was safe and tolerable in patients with malignant tumors.** **The most commonly reported side effects with probability greater than 5% include: rash, pyrexia, anemia, diarrhea, nausea, decreased appetite, platelet count decreased, white blood cell count decreased, neutrophil count decreased, nephritis, hepatic function abnormal, and hypothyroidism.** **Adverse events related to the study drug reported in these studies which are serious, fatal and life-threatening include: pyrexia, myocarditis, platelet count decreased, neutrophil count decreased, white blood cell count decreased, pneumonitis, hepatic function abnormal, colitis, pancreatitis, and renal impairment.** **More detailed information about the known and expected risks of HLX10 can be referred to in the Investigator's Brochure.**	

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2.3.3 Overall benefits: risk and ethical assessment	**Based on the current study data of HLX10, only 2 subjects experienced DLTs (1 subject received HLX10 monotherapy [3 mg/kg] once every 2 weeks, and 1 subject received HLX10 [3 mg/kg] combined with HLX04 [5 mg/kg] once every 2 weeks), the MTD was not reached yet.** ~~No dose-limiting toxicity was observed based on the current first-in-human study data for HLX10, and t~~**T**he available safety data and ~~pharmacokinetic~~**PK** data demonstrate**d** that the safety of HLX10 in patients is acceptable **and adequate** ~~enough~~ to support the implementation of this phase **III** ~~of the~~ clinical study.	Add the latest reported clinical study results.
4.3 Justification for Dose	Based on the results of the ~~HLX10~~ preclinical and **clinical** ~~phase I clinical~~ trials **of HLX10**, the currently available PK and ADA data support **HLX10 4.5 mg/kg based on mean body weight,** ~~an average body weight dose of HLX10 of 4.5 mg/kg~~ administered every 21 days as the recommended dose for phase III clinical stud**y**~~ies~~. Results of Dose Exposure Response analysis demonstrated both 4.5 mg/kg every three weeks and 3.0 mg/kg every two weeks were oversaturated doses. Given the fact that no ~~maximum tolerated dose (~~MTD~~)~~ was observed in anti-PD-1 antibodies and the European Medicines Agency~~EMA~~ and FDA approved oversaturated doses for nivolumab (nivo) and pembrolizumab (pembro) in clinical practice across multiple tumor types, Henlius believes that 4.5 mg/kg every three weeks or 3.0 mg/kg every two weeks is justified and safe.	Updates based on POL PA V2.1.
8.1 Tests and Evaluations during the Study 8.2.2 Treatment Period 8.3 Study Assessments	Section 8.1 Tumor imaging Images will be assessed by the IRRC according to RECIST v1.1 (see Appendix 2-1: Response Evaluation Criteria in Solid Tumors (RECIST 1.1)) ~~and iRECIST criteria (see~~ Appendix 2-2: iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics ~~immunotherapeutics)~~.	To clarify that IRRC will only be assessing based on RECIST 1.1 and investigator will assess based on RECIST 1.1 and iRECIST.

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	The investigator ~~and IRRC respectively~~ assesses the tumor images according to RECIST 1.1 **and iRECIST** (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation. **The IRRC assess the tumor images according to RECIST 1.1.** At the EOT visit, if tumor imaging has been performed within the last 4 weeks, a re-test is not required. **Note: For all tumor imaging timepoints, investigator must assess all the tumor images according to RECIST 1.1 and iRECIST.** Section 8.2.2 Initial treatment visit The investigator ~~and IRRC~~ should assess the tumor images according to RECIST 1.1 **and iRECIST** (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation. **The IRRC should assess the tumor images according to RECIST 1.1.** Post-PD treatment visit The investigator should assess the tumor images according to RECIST 1.1 **and iRECIST** (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation. Section 8.3	

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	Except overall survival, other efficacy endpoints are evaluated based on tumor response as per RECIST 1.1 **and iRECIST**.	
8.2.1 Screening Period (day -28 to day -1)	**Note: All reports from diagnostic procedures, which were performed before the ICF is signed and as part of the standard of care in the region and the examination methods/devices meet the study requirements might be used for the eligibility evaluation during the screening. This option restricted to those cases only, where the patient has given written confirmation that he/she consent to use his/her diagnostic reports of performed procedures before the date of ICF signature for eligibility evaluation of the actual study.**	Updates per NtF for PA V3.0.
6.2 Dosing Regimen Preparation/Handling/Storage/ Accountability	The infusion of investigational product is completed between 30 mins and 90 mins if there is not any infusion reaction. **The diluted drug solution is recommended to be used within 6 hours of preparation and has been shown to be stable for up at 24 hours. The diluted drug solution needs to be stored at approximately 2-8 °C for no longer than 24 hours and be kept from light if not used within 6 hours.**	Updates per IB 4.0 following stability testing.
1.1 Synopsis 6.6 Dose Modification	Section 1.1 In the event of intolerance to etoposide/carboplatin, the dose can be modified **twice** according to the etoposide/carboplatin prescribing information and local standard-of-care. **Once reduced, the dose cannot be increased back to 100%.** If treatment is delayed due to intolerance to chemotherapy, chemotherapy may be delayed to the next cycle of administration, with the maximum permissible interval for chemotherapy not exceeding 6 weeks. Section 6.6	Alignment of 'principles for chemotherapy modification' text between sections and removal of dose modification table for chemotherapy as in practice, the dose of carboplatin would be re-calculated before each dose.

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	Principles for chemotherapy dose modifications In the event of intolerance to etoposide/carboplatin, doses may be adjusted twice in accordance with the prescribing information of carboplatin and etoposide, **<u>the investigator's decision based on the subject's safety,</u>** and local treatment standard~~s~~ **<u>practice</u>**. Once reduced, the dose cannot be increased back to 100%. ~~**Table 1: Principles for Chemotherapy Dose Modifications Toxicity**~~ ~~**Dose Level** / **Etoposide Dosing Regimen** / **Carboplatin Dosing Regimen**~~ ~~Starting Dose / 100 mg/m^2; IV infusion on Day 1, 2 and 3 of each 3-week (21-day) cycle. / AUC = 5, up to a dose of 750 mg, IV infusion on Day 1 of each 3-week (21-day) cycle.~~ ~~First Dose Reduction / 75% of starting dose / 75% of starting dose~~ ~~Second Dose Reduction / 50% of starting dose / 50% of starting dose~~ ~~AUC=area under the concentration-time curve; IV=Intravenous~~	
5.1 Inclusion Criteria #12	≤ 1.5×ULN; In case of > 1.5 × ULN, creatinine clearance ≥ **<u>50</u>**~~60~~ mL/min	Decrease the value of creatinine clearance as per a request from the EMA
8.2.2 Treatment Period	The tumor image used to determine disease progression can be used as the new baseline image for the post-PD treatment period if 1) **<u>within</u>** 28 days prior to receiving the first dose of HLX10 or placebo therapy and 2) No study treatment between the image and first dose of HLX10 or placebo therapy, otherwise a new baseline image must be performed prior to HLX10 or placebo treatment.	Clarification that the tumor image can be used within 28 days

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
8.4.7. Pregnancy	Each fertile subject shall take appropriate contraceptive measures in a period from signing ICF through at least 6 months after the final dose of the study drug~~, and in at least 6 months after the final dose of chemotherapy drug~~.	Update of information regarding contraceptive measures
6.6 Dose Modifications	Hematological toxicities Table 1 ANC < 0.5 $\times 10^9$/L and PLT ≥ 50 $\times 10^9$/L: 75% of the **planned** ~~previous~~ dose PLT < 50 $\times 10^9$/L, regardless of ANC: 75% of the **planned** ~~previous~~ dose PLT < 50 $\times 10^9$/L with Grade 2 hemorrhage, regardless of ANC: 50% of the **planned** ~~previous~~ dose ANC < 1$\times 10^9$/L with fever ≥ 38.5 °C: 75% of the **planned** ~~previous~~ dose Non-hematological toxicities Table 2 Modified carboplatin dose by % of **planned** ~~previous~~ dose[a]	To add flexibility for investigational sites to apply dose reduction based on their standard clinical practice
8.4.1.4 Death	• Any death **(**confirmed to be PD-induced **or non-PD-induced)** should be reported as an SAE **and the death should not be reported as a separate event. The SAE report needs to be submitted** ~~and reported~~ to the clinical research associate (CRA)/clinical site manager (CSM), the sponsor, or a representative of the sponsor within 24 hrs. • ~~When a death is not (or not explicitly) due to PD, the AE resulting in this death has to be deemed as an SAE and reported to the CRA/CSM, the sponsor, or a representative of the sponsor in 24 h. The primary cause of death should be provided.~~	Rewording to avoid possible misunderstanding

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
8.4.2 Serious Adverse Events	2) Life-threatening (AE occurrence leads to an immediate risk of subject death, not including those AEs that may lead to death after PD~~, e.g., drug-induced hepatitis without liver failure~~)	Update as per ICH-E2A
8.4.4 Reporting of SAEs	The sponsor ~~is legally liable to inform~~ **has a legal responsibility to notify both the** local regulatory authority and other regulatory ~~bodies~~ **agencies about the** ~~of~~ safety ~~information of the study drug~~ **of a study intervention under clinical investigation**. The ~~investigator~~ **sponsor** ~~is legally obliged and ethically responsible to report promptly SAEs to relevant regulatory bodies and health authority, the ethics committee, and the study contact specifically in charge of receiving SAE reports, and make sure safety of other subjects is guaranteed~~ **will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators**. The investigator or any person-in-charge required by local authority shall abide by local regulatory regulations on SAE reporting and report SAEs to regulatory bodies, Institutional Review Board (IRB) or Independent Ethics Committee (IEC)**, as per request**.	Updated to meet cross-countries' requirement
9.5.1 Independent Data Monitoring Committee (IDMC)	The IDMC will be established to independently oversee the blinded sample size re-estimation procedure;	Correction of typographical error
9.5 Interim Analyses	An IDMC will be established for this study for ~~blinded~~ interim analysis. This study plans to carry out an interim analysis.	Correction of text as the interim analysis will not be blinded
6.3 Measures to Minimize Bias: Randomization and Blinding	The blinding will be performed by the ~~Data Management and~~ Statistical Unit during study treatment.	Deletion of Data Management, as blinding process is not created by

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		the Data Management function.
7. Discontinuation of Study Intervention and Participant Discontinuation	7 Discontinuation of Study Intervention**,** ~~and~~ Participant Discontinuation**, and Study Termination** Section 7.1.1 Reasons for Premature Discontinuation 1. Poor **subject** compliance that has affected the efficacy and safety evaluation; 2. **The occurrence of** AEs or SAEs **in the subjects, who are deemed unsuitable to** ~~that are inappropriate to~~ continue **receiving** the study **drug** treatment as judged by the investigator; 3. Evidence of **clear disease** ~~unequivocal~~ progression or worsening of the disease; 4. A delayed ~~dosing of the~~ study drug **administration** meeting the criteria **specified in the protocol**; 5. **Subject lost** ~~loss~~ to follow-up or death **during treatment**; 6. **Subject decided to** ~~W~~withdrawal ~~of~~ informed consent; **7. Subject decides to discontinue treatment;** 8. Other reasons of discontinuation as determined by the investigator in the best interest of the subject. Section 7.1.2 Management of premature discontinuations The reasons for premature discontinuations shall be documented in the eCRF **by the investigator**.	Updates for clarity of language and provide further detail for subjects discontinuing treatment

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	All subjects who discontinue the trial prematurely (except patients who withdraw informed consent) **and agree to continued follow-up of associate clinical outcome information,** shall undergo an EOT visit and be followed up for safety **and survival**. **See Section 8.2.4 for assessments during the follow-up period.** Subjects who discontinue the trial for reasons other than disease progression **and agree to continue follow-up of associated clinical outcome information** should be radiologically followed up until disease progression, withdrawal of informed consent, death or start of a new antineoplastic therapy. All AEs present at the time of discontinuation must be followed up until the outcomes of such AEs. In case of an enrolled subject's withdrawal for any reason~~s~~, no subject replacement is permitted. **7.4 Premature Termination of Study and Site Closure** **The study may be terminated prematurely for the reasons described below, and the premature termination of the study must be approved in writing by both the principal investigator and the Sponsor, and the results of the study should be reported as required by the protocol.** **1. The study is unlikely to be completed within an acceptable time frame due to difficult enrollment of subjects;** **2. The investigator doubts the safety of the drug during the study, and believes that continuing the study will bring serious risks to the subjects;**	

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	3. <u>The principal investigator and the Sponsor believe that it is necessary to terminate the study prematurely based on the number of AEs and their severity;</u> **4. <u>The expected efficacy cannot be reached, and it is not necessary to continue the clinical study;</u>** **5. <u>Withdrawal of the study by the drug regulatory authority;</u>** **6. <u>The Sponsor has the right to decide to terminate the study in a study site if the following occurs:</u>** • **<u>Serious violation of International Conference on Harmonization Good Clinical Practice (ICH-GCP) by the study site</u>** • **<u>Multiple serious protocol violations by the study site</u>** **<u>After termination of the study, all study-related records should be retained for reference.</u>**	
Section 5.2 Exclusion criteria Section 7.2 Participant Discontinuation/Withdrawal from the Study	Section 5.2 16. Treatment with live vaccines **<u>and all COVID-19 vaccines (fully administered to the required number of doses)</u>** within 28 days prior to study drug administration; inactivated viral vaccines for seasonal influenza are allowed. 18. Any active infection requiring systemic anti-infective therapy within 14 days prior to study drug administration **<u>or subjects with a positive RT-PCR test for SARS-CoV-2 infection at randomization. Subjects with a history of COVID-19 infection must have a negative RT-PCR test prior to the first dose of the study drug.</u>** Section 7.2 **<u>If a subject develops fever or symptoms suspected of being a result of COVID-19 during the study, they will be instructed to follow-up</u>**	Addition of information relating to subjects with or a history of COVID-19 infection

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	with their regular healthcare provider or follow the instructions for suspected COVID-19 cases per their local health authority. A subject will discontinue treatment based on discussion with the Sponsor and Medical Monitor under the following circumstances: any suspected or confirmed COVID-19 case will be immediately discontinued from study treatment for up to 12 weeks after the last study drug administration; subjects who recover from the infection within 12 weeks from the last study drug administration, can continue treatment following Sponsor's confirmation.	

Overall Rationale for the Amendment 2:

Protocol Version 2.0 was updated to Version 3.0 based on the comments from the European Medicines Agency and the United States Food and Drug Administration as part of Scientific Advice procedures.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
1.1 Synopsis 3 Objective and Endpoint Primary Efficacy Endpoint	• ~~Progression-free survival (PFS) (assessed by the independent radiology review committee [IRRC] based on Response Evaluation Criteria in Solid Tumors [RECIST] 1.1)~~ • **Overall survival (OS)**	OS is the recommended primary endpoint as 2-year survival for ES-SCLC is less than 5% and there is a limited activity in second-line therapies.
1.1 Synopsis 3 Objective and Endpoint Secondary Efficacy Endpoint	• ~~Overall survival (OS)~~ • **Progression-free survival (PFS) (assessed by the independent radiology review committee [IRRC] based on Response Evaluation Criteria in Solid Tumors [RECIST] 1.1)**	Change PFS to a secondary endpoint

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
1.1 Synopsis 4.1 Overall Design	**Initial t**~~T~~reatment should be discontinued when they have evidence of disease progression as assessed by RECIST ~~v~~1.1. ~~However, considering the limited availability and efficacy or greater toxicity of treatment options after withdrawal, and for better adaptation to standard clinical practice,~~ **If a subject has 1st disease progression and is clinically stable, and tends to receive 2nd line chemotherapy treatment subsequently (the selection of 2nd line chemotherapy may refer to the NCCN guidelines or the ESMO guidelines), it is at the discretion of the investigator to continue treating the subject with blinded HLX10 or placebo assignment per protocol in addition to the 2nd line chemotherapy, until the 2nd disease progression ~~lost clinical benefit~~, intolerable toxicity, death, withdrawal of consent, or lost to follow-up. Subjects who permanently discontinue initial treatment due to an adverse event, withdrawal of consent, or for any reason other than disease progression, will not be eligible for the post-PD treatment.** ~~the s~~**Subjects who meet**~~s all~~ **the following conditions may continue the treatment** ~~and~~ **after appropriate discussion with the subject and obtaining the supplementary informed consent.** **1. Subjects who had received HLX10 or placebo in combination with chemotherapy, who may benefit from continuing HLX10/placebo treatment despite progression, will be able to receive HLX10 or placebo therapy in the post-PD treatment.** ~~1. With no clinical signs and symptoms (including worsening of laboratory findings) indicating a significant disease progression.~~ **2. Subjects eligible for continued treatment in the post-PD treatment period, as judged by the investigator.** ~~2. A stable Eastern Cooperative Oncology Group (ECOG) performance status score.~~	In combination with second-line chemotherapy in the post-PD treatment period, subjects are prevented from being exposed to placebo alone.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	<u>3. The subject should sign the supplementary informed consent form to receive investigational product with 2nd line chemotherapy.</u> **<u>4.The subject is clinically stable, defined as:</u>** **<u>a) With no clinical signs and/or symptoms (including worsening of laboratory findings) that might indicate disease progression.</u>** **<u>b) A stable Eastern Cooperative Oncology Group (ECOG) performance status score.</u>** **<u>c) No rapid disease progression or tumor progression requiring urgent alternative medical intervention at critical anatomical sites (e.g., spinal cord compression).</u>** ~~3. No rapid disease progression or tumor progression requiring urgent alternative medical intervention at critical anatomical sites (e.g., spinal cord compression).~~ ~~4. The major organ function meets the inclusion and exclusion criteria of this study.~~ ~~5. The subject should sign the supplementary informed consent form to continue treatment.~~ ~~The primary objective of this study is to compare the PFSs of HLX10 in combination with chemotherapy versus placebo in combination with chemotherapy, as assessed by an Independent Radiology Review Committee (IRRC) using RECIST v1.1.~~	
1.1 Synopsis Treatment Groups and Duration: 8.2.2 Treatment Period	This study is divided into three periods: Screening period (28 days), treatment period **<u>(initial treatment and post-PD treatment [Optional]</u>**, until **<u>disease progression</u>** ~~loss of clinical benefit,~~ death, intolerable toxicity, withdrawal of informed consent, or occurrence of other reasons specified in the protocol, whichever occurs first), and Follow-up period (including safety follow-up and survival follow-up).	Adjustment of treatment periods because of the addition of post-PD treatment.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
1.1 Synopsis Other study drugs: combined chemotherapy 4.1 Overall Design 6.2 Dosing Regimen Preparation/Handling/Storage/Accountability 6.6 Dose Modification	Carboplatin: Area under the concentration-time curve (AUC) = 5, IV infusion, on Day 1 of each cycle up to a dose of ~~800~~**750** mg. **On Day 1, etoposide shall be administered following infusion of carboplatin.**	To adjust the maximum dosage of carboplatin according to the NCCN Chemotherapy Order Templates about Maximum Carboplatin Dose Calculation. To clarify the order of drug administration.
1.2 Schema	Screening period: **The maximum screening period is 28 days**. ~~At least 28 days.~~ Treatment period: **Including initial treatment and post-PD treatment (optional)** **After finishing the initial treatment period, patients in both arms who had 1st disease progression per RECIST 1.1 and might benefit from their assigned treatment in addition to 2nd line chemotherapy, may be eligible to continue to receive their assigned treatment in the post-PD treatment period (Optional) until the 2nd disease progression, intolerable toxicity, death, withdrawal of consent, or lost to follow-up.** Safety follow-up period: 90 days after the last **study drug administration** ~~dose~~. Safety visit is required at the site 30 days (±7 days) after the last **study drug administration** ~~dose~~, and telephone follow-up is required 90 days (±7 days) after the last **study drug administration** ~~dose~~. Survival follow-up period: Every 12 weeks ± 7 days	To keep the study periods consistent throughout the protocol.
1.3 Schedule of Activities (SoA)	~~**Study Procedures**~~ **Initial Treatment Period and Post-PD Treatment Period (Optional)**	To keep the study periods consistent throughout the protocol.

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1.3 Schedule of Activities (SoA) Initial Treatment Period footnote #7	~~Re-assessments~~ **Quality of life assessment could be performed either on Day -7 to Day -1 of the screening period or prior to dosing in Cycle 1** ~~are not required for subjects who had a quality of life assessment on Day -7 to Day -1 of the screening period.~~	To clarify the acceptable time window for performing quality of life assessment during the screening period.
1.3 Schedule of Activities (SoA) Initial Treatment Period footnote #8	**Adding footnote #8: Re-assessments prior to dosing in Cycle 1 are not required for subjects who had 12-lead ECG and ECOG scores assessment on Day -7 to Day -1 of the screening period**	To clarify the acceptable time window for performing 12-lead ECG and ECOG scores assessment during the screening period.
1.3 Schedule of Activities (SoA) Initial Treatment Period footnote #9 8.1 Tests and Evaluations during the Study	~~If the change in the subject's body weight from baseline during the study is ≤10%, dose adjustment of investigational product study drug will not be required, and if the weight change is >10%, the dose of study drug must be recalculated.~~ **If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose of investigational product, the dose of investigational product must be recalculated. All doses should be rounded to the nearest milligram.**	To substitute "study drug" with "investigational product" as investigational product stands for HLX 10/placebo only and does not include chemotherapy drugs. Language has been edited to make the dose modifications of investigational product clearer.
1.3 Schedule of Activities (SoA) Initial Treatment Period footnote #12 8.1 Tests and Evaluations during the Study Laboratory Tests	12.**serum** biochemistry items include blood urea/urea nitrogen, creatinine, sodium, potassium, magnesium, chloride, ~~carbon dioxide binding capacity or bicarbonate or total carbon dioxide~~, calcium, phosphorus, blood glucose, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase, total cholesterol, total protein, albumin; **coagulation test consist of prothrombin time (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR); myocardial enzymogram detection includes troponin-I, creatine kinase isoenzyme (CK-MB) and myoglobin**;	To delete "carbon dioxide binding capacity or bicarbonate or total carbon dioxide" from the serum biochemistry test as these items are not required but can be performed if considered standard of care in the region.

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	urinalysis items include specific gravity, urine leukocytes, pH, urine glucose, urine protein, ketone body and ~~blood cells~~**urine occult blood, microscopic examination of white blood cells and red blood cells should be collected if urine leukocytes and urine occult blood are out of normal range.** Can be performed within 3 days before dosing in each cycle; for aforementioned laboratory tests scheduled on the same day as study treatment, the study treatment can be arranged only after the test results are obtained. **For laboratory tests from the screening period completed on Day -7 ~ Day -1, it is not necessary to repeat the test again before the first administration (C1D1).** For combined chemotherapy, routine blood tests should be performed on Day 8 (± 3 days) of each treatment cycle to closely monitor bone marrow suppression.	To include myocardial enzymogram detection to address safety concern. Language has been added to clarify the urinalysis items. To clarify time window of local lab test at screening period.
1.3 Schedule of Activities (SoA) Initial Treatment Period footnote #14 8.1 Tests and Evaluations during the Study Laboratory Tests	**Patients with HBsAg (+) and/or HBcAb (+)** ~~HBsAg positive subjects~~ should be further tested for hepatitis B virus (HBV) DNA titer; and HCV antibody positive subjects should be further tested for HCV RNA.	Language has been edited to clarify the HBV testing requirements.
1.1 Synopsis 9.2 Sample Size Determination 9.5 Interim Analyses	Number of Participants: Approximately ~~489~~**567** (~~326~~ **378** for HLX10 and ~~163~~**189** for placebo). Corresponding wording and recalculation were applied to section 9.2 and 9.5	Sample size was recalculated due to change of primary endpoint to OS.
2.2.2 Clinical Study of HLX10	**Phase I clinical trial of HLX10: A prospective, open-label, dose-escalation study of HLX10 in patients with metastatic or recurrent solid tumors who had failed standard therapy. Bayesian optimal interval design (BOIN) was used to determine the maximum tolerated dose (MTD) of HLX10. The objective of this study was to evaluate the safety, PK characteristics, biomarkers, PD markers,**	To make the description of phase I study clearer.

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	<u>immunogenicity and preliminary efficacy of the study drug. Eligible subjects who meet the inclusion criteria in the screening period will receive infusion of HLX10 at a dose level specified in the protocol once every 2 weeks until disease progression, or up to one year, withdrawal from study, or death, whichever occurs first. Each treatment cycle consists of two doses of study drug, once every 2 weeks. The trial is currently ongoing. The enrollment of patients into the 0.3, 1, and 3 mg/kg groups has been completed, and the safety evaluation is ongoing.</u> ~~for a dose escalation phase I clinical trial. There are four dose groups (0.3, 1, 3 and 10 mg/kg, once two weeks) in the trial, with a maximum enrollment of about 30 subjects. At present, three patients in the fourth dose group have completed the enrollment, and no dose-limiting toxicity was observed in all dose groups during the dose-limiting toxicity observation period.~~	
4.1 Overall Design	The primary endpoint of this study is to compare the **OS** ~~PFSs~~ of HLX10 in combination with chemotherapy versus placebo in combination with chemotherapy~~, as assessed by an IRRC using RECIST v1.1 as evaluation criteria~~.	Change OS to primary efficacy endpoint.
4.1 Overall Design Figure 1: Schematic of study treatment	**<u>1st</u>** Disease Progression ~~The subject should re-consent and meet the following conditions:~~ **<u>The subject (tending to receive 2nd line chemotherapy treatment subsequently) should re-consent and meet the following conditions: (1) Subjects who had received HLX10 or placebo in combination with chemotherapy, who may benefit from continuing HLX10/placebo treatment despite progression, will be able to receive HLX10 or placebo therapy in the post-PD treatment period</u>** ~~With no clinical signs and symptoms (including worsening of laboratory findings) indicating a significant disease progression.~~	To keep the study design consistent throughout the document.

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	(2) Subjects eligible for continued treatment in the post-PD treatment period, as judged by the investigator. ~~A stable ECOG performance status score.~~ **(3) The subject should sign the supplementary informed consent form to receive investigational product with 2nd line chemotherapy.** **(4) The subject is clinically stable.** ~~No rapid disease progression or tumor progression requiring urgent alternative medical intervention at critical anatomical sites (e.g., spinal cord compression).~~ ~~(4) The major organ function meets the inclusion and exclusion criteria of this study.~~ ~~(5) The subject should sign an informed consent form again.~~ ~~Continue the treatment until persistent disease progression, worsening of symptoms due to disease progression, or intolerant toxicities~~ **Continue the treatment until the 2nd disease progression, intolerant toxicities, death, withdrawal of consent, or lost to follow-up.** ~~Continue the treatment until persistent disease progression, worsening of symptoms due to disease progression, or intolerant toxicities~~ *** Follow-Up Period includes safety follow-up and survival follow-up. Patients who are not eligible for post-PD treatment will be followed up for safety and survival status.**	
4.2 Scientific Rationale for Study Design Rationale for Post-PD Treatment	**Patients with ES-SCLC experience rapid tumor growth, fast clinical deterioration, and have an overall poor prognosis. First-line therapy with a platinum agent and etoposide has consistently demonstrated high response rates and significant clinical benefit. However, considering the limited availability and efficacy or greater toxicity of treatment options after withdrawal, and for better adaptation to standard clinical practice, subjects may be considered for subsequent treatment assignment blinded beyond radiographic disease progression per RECIST 1.1, at the discretion of the**	To clarity the rationale for post-PD treatment.

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	investigator, after appropriate discussion with the patient and obtaining informed consent. **In addition, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because disease progression (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Related research shows that shorter treatment increases the risk of relapse or progression, and there are potential benefits to patients receiving longer IO (Immunotherapy) treatment[21]. Because of the potential for pseudoprogression/tumor-immune infiltration, this study will allow patients to remain on treatment after apparent radiographic disease progression per RECIST 1.1, provided all criteria meet post-PD treatment conditions.**	
4.4 End of Study Definition	**"**The end of the study, defined as the final analysis of ~~PFS~~ **OS,** will be performed when a target number of ~~PFS~~ **OS** events (approximately ~~336~~**342**) are observed..."	To redefine End of Study due to change of primary endpoint
5.1 Inclusion Criteria #2	Male or female **aged ≥ 18** ~~between 18 to 75 (inclusive)~~ years at the time of signing the ICF.	Remove upper age limit as patients older than 75 years represent a substantial proportion of patients with ES-SCLC.
5.1 Inclusion Criteria #6	Note: Measurable lesions are not from previously irradiated sites. If the lesion at the previously irradiated site is the only selectable target lesion, **a radiological assessment showing significant progression of the irradiated lesion should be provided by the investigator.** ~~anteroposterior images showing significant progression of the lesion should be provided by the investigator.~~	Wording re-edit.

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5.1 Inclusion Criteria #12	≤ 1.5×ULN; In case of > 1.5 × ULN, creatinine clearance ≥ **60**~~50~~ mL/min	Increase the value of creatinine clearance to take into account the renal toxicity of carboplatin.
5.1 Inclusion Criteria #13	Agree to use birth control methods with an annual failure rate of <1% or maintain abstinence (avoid heterosexual intercourse) (from the signing of informed consent form (ICF) to at least **6 months** ~~120 days~~ after the final dose of study drug ~~or at least 150 days after the final dose of chemotherapy drug~~) (birth control methods with an annual failure rate of <1% include bilateral tubal ligation, male sterilization, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine contraceptive devices and copper containing intrauterine contraceptive devices or condoms)	Extending of time limits of using birth control methods or maintain abstinence after the final dose of study drug
5.1 Inclusion Criteria #14	Male patients must: agree to abstinence (avoid heterosexual intercourse) or take contraception measures as follows: male patients with a pregnant partner or a partner with of childbearing potential must remain abstinent or use a condom to prevent embryonic exposure during **study treatment** ~~chemotherapy treatment (carboplatin or etoposide)~~ and for at least ~~150 days~~**6 months** after the last dose of **study drug** ~~chemotherapy~~. Periodic abstinence (e.g., contraceptive methods based on calendar day, ovulation, basal body temperature or post-ovulation) and external ejaculation are ineligible methods of contraception.	Extending of time limits of abstinence or use a condom to prevent embryonic exposure after the last dose of study drug.
6.2 Dosing Regimen Preparation/Handling/Storage/Accountability	Other study drugs: chemotherapy • Etoposide: 100 mg/m^2, IV infusion, on Days 1, 2, and 3 of each cycle. **On Day 1, etoposide shall be administered following infusion of carboplatin.**	To clarify the order of adminstration of study drugs
6.5 Concomitant Therapy	**6.5.3 Subsequent Anti-Cancer Therapy Status**	Adding subsequent anti-cancer therapy status, to

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	The investigator or his/her qualified designee will review all new anti-cancer therapy initiated after the discontinuation of trial treatment. If the subject continues the post-PD treatment, he/she must choose to receive 2nd line chemotherapy. The preferred 2nd line chemotherapy was determined by the investigators following the NCCN /or ESMO guidelines and communicated as such to the subjects who chose to continue the Post-PD treatment. Any other anti-PD1 and anti-PD-L1 therapy are not allowed.	clarify the concomitant therapy in post-PD treatment
6.6 Dose modification	In the event of intolerance to etoposide/carboplatin, doses may be adjusted twice in accordance with the prescribing information of carboplatin and etoposide and local treatment standards. **Once reduced, the dose cannot be increased back to 100%.** Make adjustment in" Non-hematological toxicities" in both text and table for recommended carboplatin dose modification	To make adjustment to recommended dose modification.
7.1.2 Management of premature discontinuations	All subjects who discontinue the trial prematurely **(except patients who withdraw informed consent)** shall undergo an EOT visit and be followed up for safety.	To exclude subjects who withdraw their informed consent from the EOT visit and safety follow-up.
8.2.4 Follow-Up period	During the survival follow-up period, subjects ~~without PD and not receiving any other anti-tumor therapy~~ should ~~return to the hospital according to the established schedule for radiologic assessment~~ **should be followed up** until ~~PD, initiation of a new anti-tumor therapy,~~ ICF withdrawal, death, **the patient is lost to follow-up, study termination by the sponsor,** or study completion, whichever occurs first~~.; while subjects experiencing PD or undergoing any other anti-tumor therapy just need to be followed up for survival status by telephone call once every 12 weeks (±7 days).~~	To update the condition of survival follow up

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8.4 Safety Assessment	The structure and wording were re-edited, changes are listed below： 1. Any death confirmed to be PD-induced should be reported **as an SAE and reported to the clinical research associate (CRA)/clinical site manager (CSM), the sponsor, or a representative of the sponsor within 24 hrs.** ~~to the sponsor at the next monitoring visit. It should be documented but not reported as an SAE.~~ **2. Insert a section "8.4.2. 1 Drug-induced liver injury, (DILI)"** 3. **8.4.3.** Documentation of AEs. All AEs occurring in a period from signing ICF **(either main or supplementary)** through 90 days after the final administration of the study drug should be documented in corresponding AE pages in EDC. **If a subject starts a new antineoplastic therapy during the AE collection period, only information on AEs related to study treatment are documented after the new antineoplastic therapy.** The investigator shall provide all detailed information required to be completed, including date of onset, severity, action, outcome, and causality to the study drug. When collecting AE data, one has better recording diagnosis information (if possible), rather than recording a number of signs and symptoms. However, if a diagnosis is known but the patient still has other symptoms or signs not contributing to such diagnosis, then each symptom or sign should be documented separately. 4. Add AESI as follows: **AESIs are events of scientific and medical concern related to use of the investigate drug that may need to be closely monitored and communicated to sponsors by investigators. AESI can be a serious or non-serious event. The AESI expedited**	To rearrange this section according to the updated Pharmacovigilance rules.

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	report enables continuous monitoring of these events in order to describe and understand their association with the drug used in the study. **In this study, AESI include infusion reaction (infusion-related adverse reactions, IRR) and immune-related adverse events (irAE).** 5. Each fertile subject shall take appropriate contraceptive measures in a period from signing ICF through at least~~120 days~~ **6 months** after the final dose of the study drug and in at least ~~150 days~~ **6 months** after the final dose of chemotherapy drug. 6. The investigator will evaluate whether causality between the study drug and the AE is "~~definitely~~ related", "possibly related", "unlikely related", "~~definitely~~ unrelated", or "~~not evaluable~~ unknown". **AEs other than "unlikely related" and "not related" are recorded as adverse reactions.** ~~Any AE without given causality to the study drug will be deemed as "possibly related" to the study drug.~~ 7. **All AEs and SAEs that occur in each subject throughout the study should be actively followed up. Even if such events persist after discontinuation or study termination, the investigator should follow them up until all events meet any of the following criteria:** ~~All AEs occurring in a period from signing ICF through 90 days after the final dose of the study drug should be followed up until any of the following circumstances occurs:~~	
9.4.1 Efficacy Analyses	Analyses of the primary efficacy endpoint **and the secondary efficacy endpoints** will be performed for both the ITT and PPS, **mainly on the ITT**. ~~analyses of the secondary and exploratory efficacy endpoints will be performed for the ITT only.~~	To correct population for analyses due to changing of endpoints.
9.4.1.1 Analysis of primary efficacy endpoint	9.4.1.1 Analysis of primary efficacy endpoint **Overall survival (OS): Defined as a period from randomization through death regardless of causality. Data of patients without a**	To keep consistency in the document text after changing of endpoints.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
9.4.1.2 Analysis of secondary efficacy endpoints	**death record will be censored on the last known survival date.** ~~Progression free survival (assessed by the IRRC as per RECIST v1.1): PFS is defined as a period from randomization initiation to the first documentation of PD or death regardless of causality (whichever occurs first). Data of subjects with neither PD nor death will be censored on the day of the final valid tumor evaluation. Data of surviving subjects not undergoing any tumor assessment during the study will be censored on the day of randomization. Data of subjects who have no PD reported and initiate any antitumor therapy not specified in the protocol will be censored on the day of the last evaluable tumor assessment prior to the initiation of subsequent antitumor treatment.~~ The between-group comparison of **OS** ~~PFS~~ is performed by a stratified log-rank test with the following stratification factors: PD-L1 expression level (negative: TPS <1%, positive: TPS ≥1%, or not evaluable/not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years); a stratified COX proportional risk model will be used to estimate HR and its 95% CI; the Kaplan-Meier method will be used to estimate the median, and the Kaplan–Meier curve will be plotted. 9.4.1.2 Analysis of secondary efficacy endpoints **Progression free survival (assessed by the IRRC as per RECIST 1.1): PFS is defined as a period from randomization initiation to the first documentation of PD or death regardless of causality (whichever occurs first). Censor rules will be defined in SAP.** ~~Overall survival (OS): Defined as a period from randomization through death regardless of causality. Data of patients without death record will be censored on the last known survival date. Data of patients not providing any follow-up information will be censored on the randomization day.~~ The **PFS**~~OS~~ will be analyzed using the same method as that for primary efficacy endpoints.	

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
9.4.1.3 Subgroup analyses	Add the new section as 9.4.1.3 “Subgroup analyses”	To assess the consistency of the study PFS and OS, results in subgroups will be examined.
9.5 Interim Analyses	Add the stopping boundary for OS interim and final analyses	To add description per ICH-E9
10.10 Appendix 8	Replaced Appendix 8 with NCCN Guidelines®: Management of Immunotherapy-Related Toxicities (2019 V2)	To update the guidelines
Throughout the protocol	Some editorial changes were made.	To keep the consistency throughout protocol.

Overall Rationale for the Amendment 1:

The structure of protocol Version 2.0 was updated and rearranged based on Version 1.0 in accordance with ICH guidance. Additional changes made during development of Version 2.0 are clarified as follows.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
Title page	A Randomized, Double-Blind, Multicenter, Phase III Study to ~~Evaluate~~ **Compare Clinical Efficacy and Safety of** HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin-Etoposide) in Previously Untreated Patients with Extensive Stage Small Cell Lung Cancer (ES-SCLC) A short title was added.	To include the objective in the title for clarifying the purpose and objective of the study.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
Title Page, Regulatory Agency Identifying Number(s)	**NMPA Approval Document Number: 2018L02201, EudraCT Number: 2019-003063-21**	To add the NMPA approval document Number and EudraCT Number for this protocol.
Investigator Agreement Page	Updated the Agreement pages, one page for Principal Investigator, the other page for Global Coordinating Investigator.	To provide agreement pages for Principal Investigator and the Global Coordinating Investigator.
1. Protocol Summary	Inserted a header of section 1: **protocol summary**	To give an overview of the protocol.
1.3 Schedule of Activities (SoA) footnote #11 8.1 Tests and Evaluations during the Study Laboratory Tests	total cholesterol, total protein, albumin; urinalysis items include specific gravity, **urine leukocytes**, pH, urine glucose, urine protein, ketone body and blood cells.	To include urine leukocytes for urinalysis to monitor the subject's immune response.
1.1 Synopsis 3 Secondary Efficacy Objective	Progression-free survival (PFS) assessed by the investigator based on RECIST v1.1 and ~~modified RECIST criteria~~ **a modified RECIST 1.1 for immune-based therapeutics (termed iRECIST)**.	To add consensus guideline (iRECIST) developed for the use in cancer immunotherapy trials for the evaluation of PFS.
9.4.1.2 Analysis of Secondary Efficacy Endpoints	PFS assessed by the investigator as per RECIST v1.1 **and iRECIST**: Its statistical method is the same as that for primary efficacy endpoints.	
10.4 Appendix 2-2	"Modified Response Evaluation Criteria in Solid Tumors" was replaced with "iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics".	
1.1 Synopsis 3 Objectives and Endpoints	~~Exploratory~~ ~~• Exploratory population pharmacokinetic (PopPK) analysis~~	To delete the secondary objective of "Exploratory".

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
1.1 Synopsis 1.2 Shema 4.1 Overall Design 6.3 Measures to Minimize Bias: Randomization and Blinding 9.4.1.1 Analysis of primary efficacy endpoint	Randomization are stratified by PD-L1 expression level (negative**: tumor proportion scores [TPS] <1%**, positive**: TPS ≥1%**, **or not evaluable/**not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years)	To define the limits for PD-L1 expression levels specifically.
1.3 SoA footnote #8	The height measurement is performed only at screening; vital signs include body temperature, pulse, respiratory rate, and blood pressure. Body weight ~~is measured before each dose, and no dose adjustment of the study drug is required if the subject's body weight differs ≤ 10% from the reference value of the current dose during the study, otherwise the dose should be recalculated. This new body weight will serve as the baseline value for subsequent body weight measurements.~~ **Body weight will be measured prior to drug administration at each treatment cycle. If the change in the subject's body weight from baseline during the study is ≤10%, dose adjustment of study drug will not be required, and if the weight change is >10%, the dose of study drug must be recalculated.**	To clarify the timing of bodyweight measurement to allow an adjustment of the administration dose.
1.3 SoA footnote #16	**Patients must provide tumor tissues that meet the requirements for the determination of PD-L1 expression levels. It is recommended to provide formalin-fixed tumor tissue samples, paraffin-embedded tumor specimens (preferred), formalin-fixed paraffin embedded (FFPE), tumor specimens or newly prepared unstained serial tissue sections (preferably adhesive slides) within 6 months prior to the first dose of study medication. A relevant pathology report must also be provided for the above specimens.** ~~To the extent possible, formalin-fixed paraffin-embedded (FFPE) tumor samples (paraffin~~	To clarify the tumor tissue assessment procedure and purpose.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	~~blocks or unstained sections) collected at or after the diagnosis of ES-SCLC and within 6 months prior to the start of study medication or pathological reports of such specimens should be provided. In case of no archived tumor tissue samples available, it is recommended to conduct a fresh tumor lesion biopsy at screening to obtain the corresponding tumor sample (the number of specimens required is based on the biopsy result). Tumor tissue sections will be used for immunohistochemical analysis to evaluate the expression level of PD-L1 in tumor cells and tumor-infiltrating immune cells and other purposes.~~ Freshly collected specimens, radical resections, core needle biopsy, excisions, incisions, punch or clamp biopsies are acceptable **(newly obtained tissues are preferred).** Fine-needle aspirations (i.e., samples that lack a complete tissue structure and provide only cell suspension and/or cell smear), brush biopsies, and cell pellet samples from pleural or peritoneal effusions are unacceptable. For detailed requirements for tissue samples, see the laboratory manual.	
3 Objectives and Endpoints	~~Primary endpoint~~ **Primary Efficacy Endpoint** ~~Secondary endpoint~~ **Secondary Efficacy Endpoint** ~~• Incidence rates of AEs and SAEs~~ ~~• Pharmacokinetics (PK): serum HLX10 concentration~~ ~~• Immunogenicity evaluation: positive anti-drug antibody (ADA) rate~~ ~~• Relationship between PD-L1 expression level, MSI, TMB in tumor tissues and efficacy~~ ~~• Quality of life assessment~~ **Safety Endpoints** **• Adverse events (AEs) (including serious adverse events [SAEs]), laboratory tests (routine blood test, blood chemistry, coagulation function, urinalysis, thyroid function), 12-lead**	Endpoints classification were re-organized for better readability and to ensure the clarification of the endpoints.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	electrocardiogram (12 lead ECG), vital signs, and physical examination, etc. **PK Endpoint** **• Concentration of HLX10 in serum** **Immunogenicity Endpoint** **• HLX10 anti-drug antibody (ADA) positive rate** **Biomarker Endpoint** **• Relationship between PD-L1 expression, microsatellite instability (MSI), tumor mutation burden (TMB) in tumor tissue and efficacy.** **Quality of life assessment**	
4.Study Design	Inserted section 4.4 **End of study definition**, and description started from **"The end of the study is defined as the final analysis of PFS will be performed when a target number of PFS events (approximately 336)…etc."**	To clarify the definition of the end of the study.
5.1 Inclusion Criteria # 2	2. **Male or female between** 18 to 75 (inclusive) years at the time of signing the ICF.	To clarify the gender requirement of the subjects.
5.1 Inclusion Criteria # 7	Patients must provide tumor tissues that meet the requirements for the determination of PD-L1 expression levels. Subjects are assessed for an evaluable PD-L1 expression category (negative: **TPS <1%,** positive: **TPS ≥1%,** or **not evaluable/**not available) by the central laboratory for randomization.	To define the limits for PD-L1 expression levels specifically.
5. study population	1. Inserted section 5.3 **Lifestyle Consideration** and description of "**No restrictions are required**."	1. To clarify the concerns to the subject's lifestyle and to

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	2. Inserted section 5.4 **Screen failures** and description started from "**Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure…etc.**"	follow the common protocol template structure. 2. To clarify the definition of screen failures and the information required.
6. Study Intervention	Inserted the new header of Section 6 **Study Intervention** and description started from "**Study drug is defined as any investigational interventions, marketed products…etc**."	To clarify the definition of the study drug and to follow the common protocol template structure.
6.1 Study Interventions Administered	Name: Recombinant anti-PD-1 humanized monoclonal antibody injection (HLX10) **Formulations: Liquid** Specifications: 100 mg (10 mL)/vial	To clarify the formulation of the study drug.
6.2 Dosing Regimen Preparation/Handling/Storage/Accountability	Investigational/reference product: • HLX10: 4.5 mg/kg, IV infusion for 30 to 90 minutes, administered on Day 1 of each cycle, once every 3 weeks (21 days). • Placebo: IV infusion, administered on Day 1 of each cycle, once every 3 weeks (21 days). **The infusion of study drug is completed between 30 mins and 90 mins if there is not any infusion reaction.**	To define the completion of study drug infusion duration.
6.3 Measure to Minimize Bias: Randomization and Blinding	1.Inserted the new header of Section 6.3 **Measure to Minimize Bias: Randomization and Blinding** and description started from **"All subjects will be centrally randomized the IWRS/IVRS. Each subject will be assigned a unique number (randomization number)…etc.'** 2. Inserted subtitle of **Blinding** and the description started from. **" The blinding will be performed by the Data Management and Statistical Unit during study treatment…etc."**	To clarify the randomizing and blinding procedure to minimize bias.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
6.7 Intervention After the End of the Study	Inserted the new header of Section 6.7: **Intervention After the End of the Study** and description started from **"Subjects will receive standard of care…etc."**	To clarify the treatment subject will receive after the completion of the study and to follow the common protocol template structure.
7. Discontinuation of Study Intervention and Participant Discontinuation	Inserted the section 7.2 and 7.3. **7.2 Participant Discontinuation/Withdrawal from the Study** **7.3 Loss of Participants to Follow-Up**	To clarify the discontinuation/ withdrawal, and lost to follow- up from the Study.
8.1 Tests and Evaluations during the Study Table 5 and footnotes	Routine blood test • Basophils **(BAS&BAS%)** • Eosinophils **(EOS&EOS%)** • Lymphocytes **(LYM&LYM%)** • Monocytes **(MON&MONO%)** • Neutrophils **(NEU&NEUT%)** Biochemistry • **Fasting blood glucose (GLU)** Urinalysis • ~~Urine~~ Specific gravity (SG) • **Urine leukocytes** • Urine pH **value** • Urine protein **(U PRO)** • Urinary glucose **(U GLU)** • Ketones **(KET**) • Urine occult blood **(BLO)** • Microscopic examination of white blood cells **(U-WBC)** • Microscopic examination of red blood cells **(U-RBC)** Coagulation function • **Prothrombin time (PT) or** international normalized ratio (INR)	To update Table 5 and footnotes to clarify the variables to be collected during laboratory examination.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	• ~~Activated~~ Partial thromboplastin time (APTT) Footnote c. **Thyroid function tests will be performed during screening and within 3 days prior to drug administration every 2 treatment cycles during the treatment period** ****Routine blood test, blood chemistry, coagulation function and urinalysis must be performed at screening and within 3 days prior to drug administration every treatment cycle. When the aforementioned laboratory tests and study drug administration are scheduled on the same day, the study drug administration must be scheduled only after the test results are obtained. Routine blood tests will be performed on Day 8 (±3 days) of each treatment cycle during treatment with carboplatin, and close attention should be paid to bone marrow suppression.**	
8.1 Tests and Evaluations during the Study Tumor imaging	Imaging studies in this trial include computed tomography or magnetic resonance imaging (CT/MRI). Images will be assessed by the IRRC according to RECIST v1.1 (see Appendix 2-1 **Response Evaluation Criteria in Solid Tumors (RECIST 1.1)**) and ~~modified RECIST~~ **iRECIST** criteria (see Appendix 2-2: **iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics**).	To keep consistent with the study endpoint assessment criteria, changed from "RECIST V1.1 and modified RECIST" to "RECIST V1.1 and iRECIST".
8.1 Tests and Evaluations during the Study Biomarker sample collection	At screening, blood samples **and tumor tissue samples** must be collected for biomarkers detecting. Inserted the description started from: "**Patients must provide tumor tissues that meet the requirements for the determination of PD-L1 expression levels...etc."**	To update the requirement of tissue collection according to inclusion criteria #7.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	Deleted the description started from: ~~"As far as possible, FFPE tumor samples…etc.~~"	
9.3 Populations for Analyses	The definition of the enrolled population was added. Definition wordings of other populations including ITT set, PPS, SS and PKS were re-organized.	To clarify and define the populations to be analyzed in the study.
9.5 Interim Analysis	Wordings were re-organized.	To clarify the definition of the interim analysis.
9.5.1 Independent Data Monitoring Committee (IDMC) 10.1.3 Financial Disclosure 10.1.11 Source Documents 10.1.14 Protocol Approval and Amendment	Several sections were added.	To adhere to the ICH guidance.
10.2 Appendix 1	The version of Common Terminology Criteria for Adverse Events (CTCAE) is updated from v4.03 to v5.	To update the version of CTCAE.
10.5 Appendix 3	Quality of Life Scale EORTC QLQ-C30, EQ-5D-5L and EORTC QLQ-LC13 are updated.	To update the Quality of Life Scale.
Throughout the protocol	Some editorial changes were made.	To keep the consistency throughout protocol.

Table of Contents

Investigator Agreement Page 2

Investigator Agreement Page 3

Sponsor Signatory 4

Protocol Amendment Summary of Changes Table 5

Table of Contents 50

1 Protocol Summary 55

1.1 Synopsis 55

1.2 Schema 61

1.3 Schedule of Activities (SoA) 62

2 Introduction 74

2.1 Background 74

2.2 Study Rationale 75

2.2.1 Preclinical Study of HLX10 76

2.2.2 Clinical Study of HLX10 82

2.3 Benefit/Risk Assessment 82

2.3.1 Potential benefits 82

2.3.2 Identified and potential risks 83

2.3.3 Overall benefits: risk and ethical assessment 85

3 Objectives and Endpoints 86

4 Study Design 87

4.1 Overall Design 87

4.2 Scientific Rationale for Study Design 90

4.3 Justification for Dose 91

4.4 End of Study Definition 92

4.5 Unblinding 92

5 Study Population 92
5.1 Inclusion Criteria 92
5.2 Exclusion Criteria 95
5.3 Lifestyle Considerations 97
5.4 Screen Failures 97
6 Study Drug 98
6.1 Study Interventions Administered 98
6.2 Dosing Regimen Preparation/Handling/Storage/Accountability 99
6.3 Measures to Minimize Bias: Randomization and Blinding 101
6.4 Study Treatment Compliance 101
6.5 Concomitant Therapy 102
6.5.1 Prohibited Concomitant Therapies 102
6.5.2 Permitted Medications/Treatments 103
6.5.3 Subsequent Anti-Cancer Therapy Status 103
6.6 Dose Modification 103
6.7 Intervention after the End of the Study 107
7 Discontinuation of Study Intervention, Participant Discontinuation, and Study Termination 108
7.1 Discontinuation of Study Intervention 108
7.1.1 Reasons for Premature Discontinuation 108
7.1.2 Management of premature discontinuations 108
7.2 Participant Discontinuation/Withdrawal from the Study 109
7.3 Loss of Participants to Follow-Up 109
7.4 Premature Termination of Study and Site Closure 110
8 Study Assessments and Procedures 110
8.1 Tests and Evaluations during the Study 110
8.2 Visit schedule 119
8.2.1 Screening Period (day -28 to day -1) 119
8.2.2 Treatment Period 120

8.2.3 End-of-Treatment Visit 123
8.2.4 Follow-up Period 124
8.3 Study Assessments 126
8.4 Safety Assessment 127
8.4.1 Adverse Events 127
8.4.2 Serious Adverse Events 128
8.4.3 Documentation of AEs 131
8.4.4 Reporting of SAEs 134
8.4.5 Follow-up of AEs 135
8.4.6 Adverse event of special interest (AESI) 135
8.4.7 Pregnancy 136
9 Statistical Considerations 137
9.1 Statistical Hypotheses 137
9.2 Sample Size Determination 137
9.3 Populations for Analyses 138
9.4 Statistical Analyses 139
9.4.1 Efficacy Analyses 139
9.4.2 Safety Analyses 141
9.4.3 Pharmacokinetic Analyses 141
9.4.4 Immunogenicity Analyses 141
9.4.5 Biomarker Analyses 141
9.4.6 Analysis of Subject-reported Outcome Variables 142
9.5 Interim Analyses 142
9.5.1 Independent Data Monitoring Committee (IDMC) 142
10 Supporting Documentation and Operational Considerations 143
10.1 Regulatory, Ethical, and Study Oversight Considerations 143
10.1.1 Data Management 143
10.1.2 Regulatory and Ethical Considerations 144

10.1.3 Financial Disclosure 144
10.1.4 Informed Consent Process 144
10.1.5 Data Protection 145
10.1.6 GCP training 145
10.1.7 Data Quality Assurance 145
10.1.8 Audit 146
10.1.9 Data Management/Coding 146
10.1.10 Documentation and Retention of Study Data 147
10.1.11 Source Documents 147
10.1.12 Premature Termination of Study and Site Closure 147
10.1.13 Confidentiality and Publication Policy 148
10.1.14 Protocol Approval and Amendment 148
10.1.15 Liability and Insurance 149
10.2 Appendix 1: Common Terminology Criteria for Adverse Events 152
10.3 Appendix 2-1: Response Evaluation Criteria in Solid Tumors (RECIST 1.1) 153
10.4 Appendix 2-2: iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics 160
10.5 Appendix 3: Quality of Life Scale EORTC QLQ-C30, EQ-5D-5L, EORTC QLQ-LC13 183
10.6 Appendix 4: Eastern Cooperative Oncology Group (ECOG) - Performance Status Scale 190
10.7 Appendix 5: Fridericia Correction Formula 191
10.8 Appendix 6: Cockcroft and Gault Formula 192
10.9 Appendix 7: Heart Functional Classification of New York Heart Association 193
10.10 Appendix 8: Guidelines for Dose Modification and Treatment for Immune-Related Toxicity 194
10.11 Appendix 9: Prohibited Traditional Chinese Medicines 218
10.12 Appendix 10: Abbreviations 219
11 References 221

List of Tables

Table 1: Carboplatin Dose Modifications for Hematological Toxicities 106

Table 2: Carboplatin Dose Modifications Based on Non-Hematological Toxicities in Previous Treatments 107

Table 3: Etoposide Dose Modification for Subjects with Renal Impairment 107

Table 4: Laboratory Tests 115

Table 5: Blood Sample Collection Time Points 117

Table 6: The abnormal liver function test (LFT) needed to be reported as an SAE 130

Table 7: CTCAE Description 132

Table 8: Evaluation of Causality Between AE and Study Drug 134

Table 9 Analysis Timing and Stopping Boundary of Overall Survival 142

Table 10: Evaluation of Target Lesions 156

Table 11: Evaluation of Non-Target Lesions 157

List of Figures

Figure 1: Schematic of study treatment 89

1 Protocol Summary

1.1 Synopsis

Protocol Title: A Randomized, Double-Blind, Multicenter, Phase III Study to Compare Clinical Efficacy and Safety of HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin-Etoposide) in Previously Untreated Patients with Extensive Stage Small Cell Lung Cancer (ES-SCLC)

Sponsor Study No.: HLX10-005-SCLC301

Phase: Phase III

Sponsor: Shanghai Henlius Biotech, Inc.

Rationale:

Based on the considerable benefits of PD-1/PD-L1 inhibitors in patients with tumors, Shanghai Henlius Biotech, Inc. has developed an innovative monoclonal antibody HLX10 targeting PD-1. Based on preclinical animal studies of HLX10, it has the potential to treat a variety of different tumor types, either as monotherapy or in combination with chemotherapy. The present study is planned in previously untreated patients with ES-SCLC worldwide to compare clinical efficacy and safety of HLX10 (recombinant anti-PD-1 humanized monoclonal antibody injection) in combination with chemotherapy (Carboplatin-Etoposide).

Objectives and Endpoints

Objective	Endpoint
Primary To compare the clinical efficacy of HLX10 in combination with chemotherapy versus placebo in combination with chemotherapy in previously untreated patients with ES-SCLC.	Primary Efficacy Endpoint • Overall survival (OS) Secondary Efficacy Endpoints • Progression-free survival (PFS) (assessed by the independent radiology review committee [IRRC] based on Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) • PFS (assessed by the investigator based on RECIST 1.1 and a modified RECIST 1.1 for immune-based therapeutics [termed iRECIST]) • PFS2 (assessed by the investigator based on RECIST 1.1) • Objective response rate (ORR) (assessed by the IRRC and investigator based on RECIST 1.1) • Duration of response (DOR) (assessed by the IRRC and the investigator based on RECIST 1.1)
Secondary To compare the safety and tolerability of HLX10 in combination with chemotherapy versus placebo in combination with chemotherapy in previously untreated patients with ES-SCLC. To measure the exposure following HLX10 administration.	Safety Endpoints • Adverse events (AEs) (including serious adverse events [SAEs]), laboratory tests (routine blood test, blood chemistry, coagulation function, urinalysis, myocardial function and thyroid function), 12-lead electrocardiogram (12-lead ECG), vital signs, and physical examination, etc. Pharmacokinetic (PK) Endpoint • Concentration of HLX10 in serum Immunogenicity Endpoint • HLX10 anti-drug antibody (ADA) positive rate Biomarker Endpoint • Relationship between PD-L1 expression, microsatellite instability (MSI), tumor mutation burden (TMB) in tumor tissue and efficacy. Quality of life assessment

Overall Design:

This is a randomized, double-blind, placebo controlled, clinical phase III study to compare the clinical efficacy, safety and tolerability of HLX10 or placebo in combination with chemotherapy in patients with previously untreated ES-SCLC, to collect PK parameters and to investigate the biomarker related to efficacy.

Subjects in this study will be randomized to arm A or B at 2:1 ratio as follows:

- Arm A (HLX10): HLX10 + chemotherapy (carboplatin-etoposide)
- Arm B (control): placebo + chemotherapy (carboplatin-etoposide)

Randomization is stratified by PD-L1 expression level (negative: tumor proportion scores [TPS] <1%, positive: TPS ≥1%, or not evaluable/not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years).

After screening, subjects meeting the inclusion criteria and none of the exclusion criteria will be enrolled. Included subjects will be treated with HLX10 or placebo in combination with chemotherapy once every 3 weeks, until disease progression, death, intolerable toxicity, withdrawal of informed consent, or occurrence of other reasons specified in the protocol (whichever occurs first).

Initial treatment should be discontinued when they have evidence of disease progression as assessed per RECIST 1.1. If a subject has 1st disease progression and is clinically stable, and tends to receive 2nd line chemotherapy treatment subsequently (the selection of 2nd line chemotherapy may refer to the NCCN guidelines or the ESMO guidelines), it is at the discretion of the investigator to continue treating the subject with blinded HLX10 or placebo assignment per protocol in addition to the 2nd line chemotherapy, until the 2nd disease progression, intolerable toxicity, death, withdrawal of consent, or lost to follow-up. Subjects who permanently discontinue initial treatment due to an adverse event, withdrawal of consent, or for any reason other than disease progression, will not be eligible for the Post-Progressive Disease treatment.

Subjects who **meet the following conditions** may continue the treatment after appropriate discussion with the subject and obtaining the supplementary informed consent.

1. Subjects who had received HLX10 or placebo in combination with chemotherapy, and who may benefit from continuing HLX10/placebo treatment despite progression, will be able to receive HLX10 or placebo therapy in the post-PD treatment.

2. Subjects eligible for continued treatment in the post-PD treatment period, as judged by the investigator.
3. The subject should sign the supplementary informed consent form to receive investigational product with 2nd line chemotherapy.
4. The subject is clinically stable, defined as:
    a) With no clinical signs and/or symptoms (including worsening of laboratory findings) that might indicate disease progression.
    b) A stable Eastern Cooperative Oncology Group (ECOG) performance status score.
    c) No rapid disease progression or tumor progression requiring urgent alternative medical intervention at critical anatomical sites (e.g., spinal cord compression).

Number of Participants:

Approximately 567 (378 for HLX10 and 189 for placebo).

Treatment Groups and Duration:

This study is divided into three periods: Screening period (28 days), treatment period (initial treatment and post-PD treatment [Optional] until disease progression, death, intolerable toxicity, withdrawal of informed consent, or occurrence of other reasons specified in the protocol, whichever occurs first), and Follow-up period (including safety follow-up and survival follow-up).

The study drugs including HLX10/placebo and chemotherapy drugs are administered every 3-week (21-day) cycle as follows:

Investigational product: HLX10 or placebo

- HLX10, intravenous (IV) infusion, 4.5 mg/kg, administered on Day 1 of each 3-week (21 day) cycle.

The infusion of investigational product is completed between 30 mins and 90 mins if there is no any infusion reaction.

Other study drugs: combined chemotherapy

The following regimen will be given every 21-day (3-week) cycle for a maximum of 4 cycles.

- Etoposide: 100 mg/m^2, IV infusion, on Days 1, 2, and 3 of each cycle.

- Carboplatin: Area under the concentration-time curve (AUC) = 5, IV infusion, on Day 1 of each cycle up to a dose of 750 mg. On Day 1, etoposide shall be administered following infusion of carboplatin.

Refer to Figure 1 "Schematic of study treatment" for the regimen of each treatment arm. On Day 1 of dosing in each treatment cycle, subjects will be given HLX10 or placebo intravenously first, followed by intravenous carboplatin + etoposide. Vital signs will be closely monitored during the administration. HLX10 or placebo is administered via a blinded infusion, carboplatin + etoposide (up to 4 cycles) via an open-label infusion, and subjects will continue receiving etoposide on Days 2 and 3. Treatment with study drug will continue until disease progression, intolerable toxicity, discontinuation decided by subject or investigator, death, withdrawal of informed consent, pregnancy, noncompliance with protocol or procedure requirements, administrative reasons, or other reasons specified in the protocol, whichever occurs first.
If chemotherapy is not used due to toxicity or other reasons in a certain cycle, it is not counted as the number of chemotherapy cycles. After completing 4 cycles of chemotherapy, even if the subject does not meet the above criteria, the chemotherapy will not be continued.

General Principles for Dose Modification

Any modified or delayed doses should be recorded in the source document and electronic case report form (eCRF). Adverse events are assessed for severity according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

- For concomitant conditions already present at baseline, dose modifications may be determined by the investigator based on changes in severity of toxicity. For example, if the subject already has a Grade 1 weakness at baseline, and the severity increases to Grade 2 during treatment, it may be considered to make dose modification according to Grade 1 toxicity due to 1-grade increase in toxicity.
- If multiple toxicities of different severities occur at the same time, the dose should be adjusted according to the most severe toxicity.
- If the toxicity is related to one of the study drugs only (for example, HLX10, carboplatin or etoposide) as assessed by the investigator, dose modification of that study drug only with reference to the corresponding dose modification principle is acceptable, and the subject can continue receiving the other study treatment in the absence of other contraindications.
- If the toxicity is associated with only one of the chemotherapy medications as assessed by the investigator, the dose of the other chemotherapy medication may not be adjusted.

- In the event that a delay is required for reasons of toxicity (not definitively related to which drug), similar delays of all study drugs at the same time are required if recovery to a re-dosing level is expected within 2 weeks.
- If HLX10/placebo, carboplatin, or etoposide is interrupted due to toxicity, study treatment must be restarted, keeping HLX10/placebo in sync with the chemotherapy treatment cycles.

Principles for Chemotherapy Modification

In the event of intolerance to etoposide/carboplatin, the dose can be modified twice according to the etoposide/carboplatin prescribing information and local standard-of-care. Once reduced, the dose cannot be increased back to 100%.

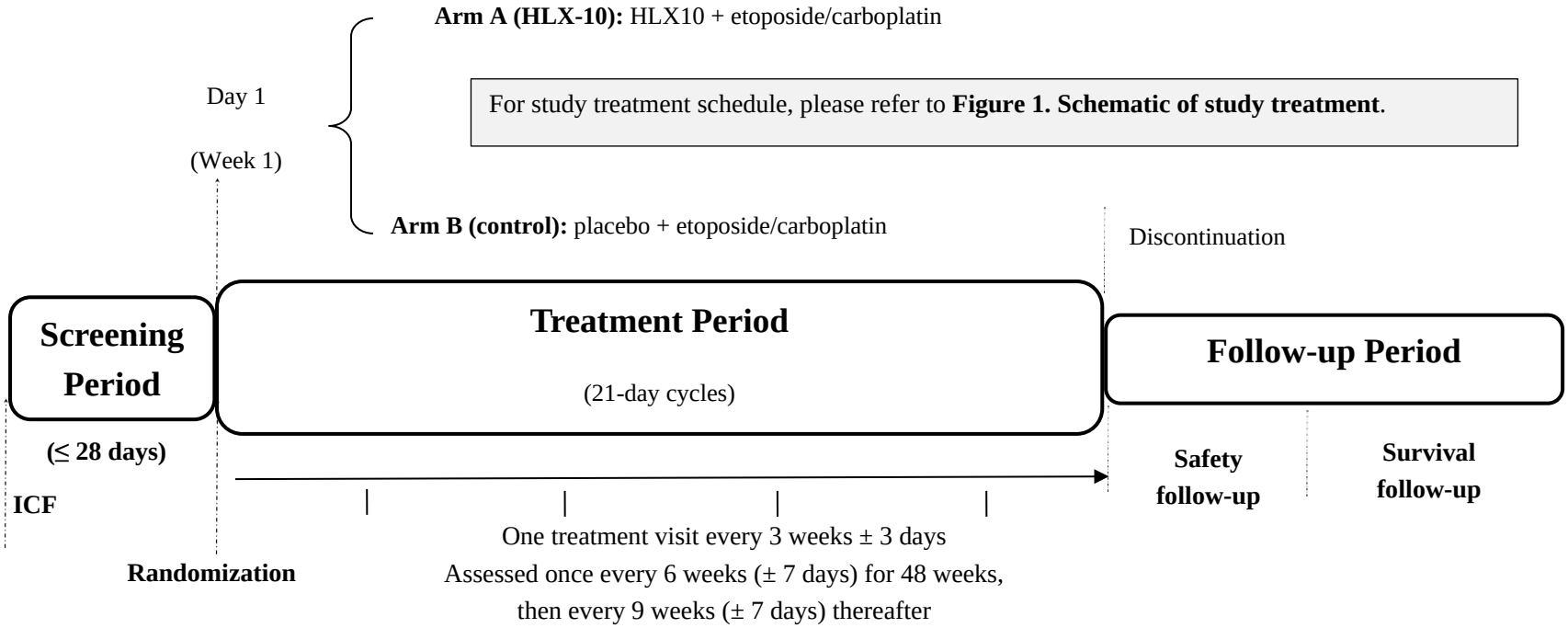
If treatment is delayed due to intolerance to chemotherapy, chemotherapy may be delayed to the next cycle of administration, with the maximum permissible interval for chemotherapy not exceeding 6 weeks.

Principles for HLX10 or Placebo Modification

In the event of HLX10- or placebo-related toxicity, a delay in HLX10 or placebo is allowed rather than dose adjustment. Subjects who miss a scheduled infusion should be actively contacted to arrange another visit as soon as possible for administration. Administration of HLX10 or placebo may be delayed, but a dosing interval of up to 12 weeks is considered intolerable of HLX10 or placebo, where HLX10 or placebo will be permanently discontinued and the subject should withdraw from the trial. For a treatment delay due to intolerance to HLX10 or placebo, chemotherapy should be administered as scheduled, and HLX10 or placebo may be postponed to the next cycle with no more than 12 weeks between doses; for a treatment delay due to intolerance to chemotherapy, chemotherapy may be postponed to the next cycle with an interval no more than 6 weeks.

1.2 Schema

Overall study design



Stratification factors:

- PD-L1 expression level (negative: TPS <1%, positive: TPS ≥1%, or not evaluable/not available)
- Brain metastasis (yes versus no)
- Age (≥ 65 years versus < 65 years)

TPS = Tumor Proportion Scores.

Screening period: The maximum screening period is 28 days.
Treatment period: Including initial treatment and post-PD treatment (optional)
After finishing the initial treatment period, patients in both arms who had 1st disease progression per RECIST 1.1 and might benefit from their assigned treatment in addition to 2nd line chemotherapy, may be eligible to continue to receive their assigned treatment in the post-PD treatment period (Optional) until the 2nd disease progression, intolerable toxicity, death, withdrawal of consent, or lost to follow-up.
Safety follow-up period: 90 days after the last study drug administration. Safety visit is required at the site 30 days (±7 days) after the last study drug administration, and telephone follow-up is required 90 days (±7 days) after the last study drug administration.
Survival follow-up period: Every 12 weeks ± 7 days.

1.3 Schedule of Activities (SoA)

Initial Treatment Period

Periods	**Screening Period**		**Treatment Period (three-week cycles)**					**End-of-Treatment (EOT) visit[1]**	**Follow-up Period[2]**	
Treatment Cycles/Visits	Screening Period		1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[3]
Time of Visit	-28 to -8	-7 to -1	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[4]				± 3	± 3	± 3	± 3	+7	± 7	± 7
Management Procedures										
Informed consent form	**X**									
Inclusion/exclusion criteria	**X**									
Dispensing of subject ID card	**X**									
Demographics and medical history	**X**									
Prior and concomitant therapies[5]	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Clinical Operations/Assessments										
Adverse events[6]	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Quality of life[7]		**X**	**X**		**X**		**X**	**X**	**X**	
Echocardiography	**X**									
12-lead ECG[8]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
ECOG scores[8]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Complete physical examination	**X**									
Symptom-oriented physical examination			**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Height, weight and vital signs[9]	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Subsequent antineoplastic therapy									**X**	**X**
Survival status			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Study Treatment										

Periods	**Screening Period**		**Treatment Period (three-week cycles)**					**End-of-Treatment (EOT) visit[1]**	**Follow-up Period[2]**	
Treatment Cycles/Visits	Screening Period		1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[3]
Time of Visit	-28 to -8	-7 to -1	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[4]				± 3	± 3	± 3	± 3	+7	± 7	± 7
Randomization[10]			**X**							
HLX10 or placebo[10]			**X**	**X**	**X**	**X**	**X**			
Etoposide + carboplatin			**X**	**X**	**X**	**X**				
Clinical Operations/Assessments: by study site										
Pregnancy test[11]		**X**			**X**		**X**	**X**	**X**	
Routine blood test, serum biochemistry, coagulation test, myocardial function (CK, CKMB, TnI/TnT) and BNP (or NT pro BNP), urinalysis[12]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
T3 or FT3, T4 or FT4, TSH[13]		**X**			**X**		**X**	**X**	**X**	
HBV antibody, HBV DNA[14]	**X**									
● In case of HBV DNA (-) and: 1) HBsAg (+), or 2) HBcAb (+) and HBsAg (-) at baseline, HBV antibody and HBV DNA should be examined during the treatment period.					**X**		**X**	**X**	**X**	
HCV antibody, HCV RNA[14]	**X**									
● In case of HCV antibody (+) and HCV RNA (-) at baseline, HCV antibody and HCV RNA should be					**X**		**X**	**X**	**X**	

Periods	**Screening Period**		**Treatment Period (three-week cycles)**					**End-of-Treatment (EOT) visit[1]**	**Follow-up Period[2]**	
Treatment Cycles/Visits	Screening Period		1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[3]
Time of Visit	-28 to -8	-7 to -1	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[4]				± 3	± 3	± 3	± 3	+7	± 7	± 7
examined during the treatment period.										
HIV	**X**									
Tuberculosis[15]	**X**									
Clinical Operations/Assessments: by central laboratory										
HLX10-PK, ADA[16]			**X**	**X**		**X**	**X**	**X**	**X**	
Efficacy Assessment										
Radiological Examination[17]	**X**				**X**		**X**	**X**		
Biomarker Sample Collection										
Tumor tissue[18]	**X**									
Blood	**X**									

ADA=anti-drug antibody, DNA=deoxyribonucleic acid, ECOG=Eastern Cooperative Oncology Group, HBcAb=hepatitis B core antibody, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, PK=pharmacokinetics, RNA=ribonucleic acid.

1. If a subject discontinues study treatment for any reason, an end-of-treatment (EOT) visit should be performed whenever possible and should be completed within 7 days after informed or discontinuation confirmed (and should be completed before the subject starts a new anti-tumor therapy);
2. All subjects are required to visit the study site for safety follow-up 30 days (± 7 days) after the last study drug administration; if the end-of-treatment visit is delayed for any reasons and occurs after the time window of 30 days (± 7 days), no further safety follow-up visit is required. All subjects are required to receive a follow-up telephone call for safety follow-up 90 days (± 7 days) after the last study drug administration. Only the information of AEs and AE-related concomitant drugs is collected.
3. Subjects should be followed for survival by telephone every 12 weeks ± 7 days after starting a new antineoplastic therapy or treatment termination criteria are met; the frequency of survival follow-up may be increased as appropriate.

Periods	**Screening Period**		**Treatment Period (three-week cycles)**					**End-of-Treatment (EOT) visit[1]**	**Follow-up Period[2]**	
Treatment Cycles/Visits	Screening Period		1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[3]
Time of Visit	-28 to -8	-7 to -1	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[4]				± 3	± 3	± 3	± 3	+7	± 7	± 7

4. The maximum screening period is 28 days; the time windows are ± 3 days for treatment, ± 7 days for tumor assessment, + 7 days for EOT visit, and ± 7 days for follow-up. ECOG performance status, serum pregnancy test, blood routine, biochemistry, coagulation, myocardial function, urinalysis and thyroid function (T3 or FT3, T4 or FT4, TSH) should be completed within 7 days before randomization, and the subjects should meet the corresponding inclusion/exclusion criteria for enrollment.
5. All prior and concomitant medications are recorded from 30 days prior to signing the informed consent form (ICF) through the safety follow-up visit; concomitant medications associated with AEs are recorded up to 90 days after the last study treatment.
6. All AEs and treatment emergent AEs are recorded from the time of signing the ICF until 90 days after the last study treatment. If a subject starts a new antineoplastic therapy during the AE collection period, only information on AEs related to study treatment are collected after the new antineoplastic therapy.
7. Quality of life scales including the EQ-5D-5L, the European Organization for Research and Treatment of Cancer Quality of Life Scale (EORTC QLQ-C30), and the European Organization for Research and Treatment of Cancer lung cancer questionnaire module (EORTC QLQ-LC13). Such scales are evaluated prior to the first dose and every other subsequent dosing cycle (i.e., pre-dose in Cycles 1, 3, 5, 7, etc.) until EOT. A quality of life assessment is required at the EOT visit if no assessment has been performed within the past 3 weeks. Quality of life assessment could be performed either on Day -7 to Day -1 of the screening period or prior to dosing in Cycle 1.
8. Re-assessments prior to dosing in Cycle 1 are not required for subjects who had 12-lead ECG and ECOG scores assessment on Day -7 to Day -1 of the screening period.
9. **The height measurement is performed only at screening**; vital signs include body temperature, pulse, respiratory rate, and blood pressure. Body weight will be measured prior to drug administration at each treatment cycle. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose of investigational product, the dose of investigational product must be recalculated. All doses should be rounded to the nearest milligram.
10. Study drug is administered on Day 1 of each 3-week cycle after all clinical and laboratory operations/assessments are completed. No more than 3 days must have elapsed between the date of randomization and the date of the first study dose.
11. Women of childbearing potential must have a serum pregnancy test. This is also performed within 3 days prior to dosing every other cycle during the treatment period.
12. Routine blood test items include red blood cell count, hemoglobin, platelet, white blood cell count, white blood cell differential counts and percentages (including: basophils, eosinophils, lymphocytes, monocytes, neutrophils); serum biochemistry items include blood urea/urea nitrogen, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, blood glucose, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase, total cholesterol, total protein, albumin; coagulation test consist of prothrombin time (PT), activated partial thromboplastin time (APTT) and

Periods	**Screening Period**		**Treatment Period (three-week cycles)**					**End-of-Treatment (EOT) visit[1]**	**Follow-up Period[2]**	
Treatment Cycles/Visits	Screening Period		1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[3]
Time of Visit	-28 to -8	-7 to -1	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[4]				± 3	± 3	± 3	± 3	+7	± 7	± 7

international normalized ratio (INR); myocardial function detection includes troponin-I (TnI)/troponin-T (TnT), creatine kinase isoenzyme (CK-MB)/ and creatine kinase (CK), Brain Natriuretic Peptide (BNP)/N-terminal pro-Brain Natriuretic Peptide (NT-pro BNP); urinalysis items include specific gravity, urine leukocytes, pH, urine glucose, urine protein, ketone body and urine occult blood, microscopic examination of white blood cells and red blood cells should be collected if urine leukocytes and urine occult blood are out of normal range. These tests should be performed **within 3 days before dosing in each cycle**; for aforementioned laboratory tests scheduled on the same day as study treatment, the study treatment can be arranged only after the test results are obtained. For laboratory tests from the screening period completed on Day -7 ~ Day -1, it is not necessary to repeat the test again before the first administration (C1D1). For combined chemotherapy, routine blood tests should be performed on Day 8 (± 3 days) of each treatment cycle to closely monitor bone marrow suppression.

13. Thyroid function tests include triiodothyronine (T3 or FT3), thyroxine (T4 or FT4) and thyroid stimulating hormone (TSH) assays. This is also performed within 3 days prior to dosing every other cycle during the treatment period.
14. All subjects are tested for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody at screening. Patients with HBsAg (+) and/or HBcAb (+) should be further tested for hepatitis B virus (HBV) DNA titer; and HCV antibody positive subjects should be further tested for HCV RNA. In case of HBV DNA (-) and: 1) HBsAg (+), or 2) HBcAb (+) and HBsAg (-) at baseline, HBV antibody and HBV DNA should be tested every 2 cycles during the treatment period. In case of HCV antibody (+) and HCV RNA (-) at baseline, HCV antibody and HCV RNA should be tested every 2 cycles during the treatment period.
15. Bulgarian subjects should be tested for active and latent tuberculosis using a method as per standard local practice (as requested by the Bulgarian Drug Agency for Bulgarian subjects).
16. PK and ADA sampling: (**Note: ADA samples will only be collected pre-dose** and procedures are described in the laboratory manual)
    - PK and ADA samples for HLX10 or placebo will be collected at the following time points: within 7 days **pre-dose** in Cycle 1, within 3 days **pre-dose** in Cycles 2, 4, 6, 8 and every 4 cycles thereafter, within 2 hours **after the end** of dosing in Cycles 1 and 8 of treatment period **(for PK only)**, at EOT visit and safety follow-up.
17. Computerized tomography (CT) or magnetic resonance imaging (MRI) should be performed at screening, every 6 weeks (± 7 days) during the first 48 weeks after the start of study treatment, and every 9 weeks (± 7 days) after week 48 on sites including brain, chest, abdomen, pelvic cavity and any other sites suspected to have tumor lesions, in which **brain MRI or CT (preferably MRI) and bone scans** are required for all subjects at screening, and are performed in the treatment period as determined by the investigator according to clinical needs (if baseline brain CT/MRI shows that brain metastasis is not present, the subject should have follow up brain imaging only

Periods	**Screening Period**		**Treatment Period (three-week cycles)**					**End-of-Treatment (EOT) visit[1]**	**Follow-up Period[2]**	
Treatment Cycles/Visits	Screening Period		1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[3]
Time of Visit	-28 to -8	-7 to -1	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[4]				± 3	± 3	± 3	± 3	+7	± 7	± 7

if clinically indicated at the discretion of the investigator. If baseline brain CT/MRI has confirmed central nervous system (CNS) metastasis, continuous brain imaging test should be carried out as part of the regular RECIST evaluation assessments); examination methods at the same site should be consistent as much as possible throughout the study; if there are no contraindications, contrast agent should be used. The investigator and IRRC respectively assess the tumor images according to RECIST 1.1 (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation. If tumor assessment has been performed within 28 days prior to the first dose by the same methods and devices in the same hospital, it may serve as the baseline tumor assessment. At the EOT visit, if tumor imaging has been performed within the last 4 weeks, a re-test is not required. For subjects who discontinued for reasons other than disease progression, radiological assessments are to be continued as scheduled, until disease progression, initiation of new antineoplastic therapy, withdrawal of ICF, death, or end of study, whichever occurs first.

18. Patients must provide tumor tissues that meet the requirements for the determination of PD-L1 expression levels. It is recommended to provide formalin-fixed tumor tissue samples, paraffin-embedded tumor specimens (preferred), formalin-fixed paraffin embedded (FFPE), tumor specimens or newly prepared unstained serial tissue sections (preferably adhesive slides) within 6 months prior to the first dose of study medication. A relevant pathology report must also be provided for the above specimens. Freshly collected specimens, radical resections, core needle biopsy, excisions, incisions, punch or clamp biopsies are acceptable (newly obtained tissues are preferred). Fine-needle aspirations (i.e., samples that lack a complete tissue structure and provide only cell suspension and/or cell smear), brush biopsies, and cell pellet samples from pleural or peritoneal effusions are unacceptable. For detailed requirements for tissue samples, see the laboratory manual.

Post-PD Treatment Period (Optional)

Periods	**Post-PD Treatment Period (three-week cycles)[1]**					**End-of-Treatment (EOT) visit[2]**	**Follow-up Period[3]**	
Treatment Cycles/Visits	1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[4]
Time of Visit	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[5]		± 3	± 3	± 3	± 3	+7	± 7	± 7
Management Procedures								
Supplementary informed consent form	**X**							
Eligibility criteria	**X**							
Concomitant therapies[6]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Clinical Operations/Assessments								
Adverse events[7]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
12-lead ECG	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Symptom-oriented physical examination	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Weight and vital signs[8]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
ECOG scores	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Subsequent antineoplastic therapy	**X**[9]						**X**	**X**

Periods	**Post-PD Treatment Period (three-week cycles)[1]**					**End-of-Treatment (EOT) visit[2]**	**Follow-up Period[3]**	
Treatment Cycles/Visits	1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[4]
Time of Visit	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[5]		± 3	± 3	± 3	± 3	+7	± 7	± 7
Survival status	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Study Treatment								
HLX10 or placebo[10]	**X**	**X**	**X**	**X**	**X**			
Clinical Operations/Assessments: by study site								
Pregnancy test[11]	**X**		**X**		**X**	**X**	**X**	
Routine blood test, serum biochemistry, coagulation test, myocardial function, urinalysis[12]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
T3 or FT3, T4 or FT4, TSH[13]	**X**		**X**		**X**	**X**	**X**	
HBV antibody, HBV DNA[14]								
● In case of HBV DNA (-) and: 1) HBsAg (+), or 2) HBcAb (+) and HBsAg (-) at baseline, HBV antibody and HBV DNA should be examined during the treatment period.	**X**		**X**		**X**	**X**	**X**	
HCV antibody, HCV RNA[14]								

Periods	**Post-PD Treatment Period (three-week cycles)[1]**					**End-of-Treatment (EOT) visit[2]**	**Follow-up Period[3]**	
Treatment Cycles/Visits	1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[4]
Time of Visit	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[5]		± 3	± 3	± 3	± 3	+7	± 7	± 7
● In case of HCV antibody (+) and HCV RNA (-) at baseline, HCV antibody and HCV RNA should be examined during the treatment period.	**X**		**X**		**X**	**X**	**X**	
HLX10-PK, ADA[15]	**X**				**X**	**X**	**X**	
Efficacy Assessment								
Radiological Examination[16]	**X**		**X**		**X**	**X**		

Periods	**Post-PD Treatment Period (three-week cycles)[1]**					**End-of-Treatment (EOT) visit[2]**	**Follow-up Period[3]**	
Treatment Cycles/Visits	1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[4]
Time of Visit	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[5]		± 3	± 3	± 3	± 3	+7	± 7	± 7

1. After finishing the initial treatment period, patients in both arms who had 1st disease progression per RECIST 1.1 who, in the investigator's opinion, would continue to receive benefit from their assigned treatment in addition to 2nd line chemotherapy may be eligible to continue to receive their assigned treatment in the post-PD treatment period (Optional) until the 2nd disease progression, intolerable toxicity, death, withdrawal of consent, or lost to follow-up. The following visits and assessments are recommended for post-PD treatment period.
2. If a subject discontinues study treatment for any reason, an end-of-treatment (EOT) visit should be performed whenever possible and should be completed within 7 days after informed or discontinuation confirmed (and should be completed before the subject starts a new anti-tumor therapy).
3. All subjects are required to visit the study site for safety follow-up 30 days (± 7 days) after the last study drug administration; if the EOT visit is delayed for any reason and occurs after the time window of 30 days (± 7 days), no further safety follow-up visit is required. All subjects are required to receive a follow-up telephone call for safety follow-up 90 days (± 7 days) after the last study drug administration. Only the information of AEs and AE-related concomitant drugs is collected.
4. Subjects should be followed for survival by telephone every 12 weeks ± 7 days after starting a new antineoplastic therapy or treatment termination criteria are met; the frequency of survival follow-up may be increased as appropriate.
5. The time windows are ± 3 days for treatment, ± 7 days for tumor assessment, + 7 days for EOT visit, and ± 7 days for follow-up. The subjects should meet the corresponding eligibility criteria for enrollment.
6. All concomitant medications are recorded up to the safety follow-up visit, and concomitant medications associated with AEs are recorded up to 90 days after the last study treatment.
7. All AEs and treatment emergent AEs are recorded up to 90 days after the last study treatment. If a subject starts a new antineoplastic therapy during the AE collection period, only information on AEs related to study treatment are collected after the new antineoplastic therapy.
8. Vital signs include body temperature, pulse, respiratory rate, and blood pressure. Body weight will be measured prior to drug administration at each treatment cycle. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose of investigational product, the dose of investigational product must be recalculated. All doses should be rounded to the nearest milligram.

Periods	**Post-PD Treatment Period (three-week cycles)[1]**					**End-of-Treatment (EOT) visit[2]**	**Follow-up Period[3]**	
Treatment Cycles/Visits	1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[4]
Time of Visit	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[5]		± 3	± 3	± 3	± 3	+7	± 7	± 7

9. Subsequent antineoplastic therapy in post-PD treatment period must be 2nd line chemotherapy. 2nd line chemotherapy (anti-PD1 and anti-PD-L1 therapy are not included) was determined by investigators after communicating with the subjects, NCCN guidelines or ESMO guidelines are the preferred reference.
10. Subjects must not initiate treatment with HLX10 or placebo in post-PD treatment any earlier than 21 days and no more than 12 weeks after their last dose of initial treatment (including chemotherapy) regardless of the time of progression. HLX10 or placebo is administered on Day 1 of each 3-week cycle after all clinical and laboratory operations/assessments are completed.
11. Women of childbearing potential must have a serum pregnancy test. This is also performed within 3 days prior to dosing every other cycle during the treatment period. If the test is done within 3 days before the first dose of investigational drug, it is not necessary to perform the test again.
12. Routine blood test items include red blood cell count, hemoglobin, platelet, white blood cell count, white blood cell differential counts and percentages (including: basophils, eosinophils, lymphocytes, monocytes, neutrophils); serum biochemistry items include blood urea/urea nitrogen, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, blood glucose, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase, total cholesterol, total protein, albumin; coagulation test consist of prothrombin time (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR); myocardial function detection (TnI/TnT, CK-MB/CK) and BNP/NT-pro BNP; urinalysis items include specific gravity, urine leukocytes, pH, urine glucose, urine protein, ketone body and urine occult blood, microscopic examination of white blood cells and red blood cells should be collected if urine leukocytes and urine occult blood are out of normal range. These are performed within 3 days before dose in each cycle; for aforementioned laboratory tests scheduled on the same day as study treatment, the study treatment can be arranged only after the test results are obtained. If concomitant chemotherapy requires additional laboratory tests, follow local clinical guidelines. If the test is done within 3 days before the first dose of investigational drug, it is not necessary to perform the test again.
13. Thyroid function tests include triiodothyronine (T3 or FT3), thyroxine (T4 or FT4) and thyroid stimulating hormone (TSH) assays. This is also performed within 3 days prior to dosing every other cycle during the treatment period. If the test is done within 3 days before the first dose of investigational drug, it is not necessary to perform the test again.

Periods	**Post-PD Treatment Period (three-week cycles)[1]**					**End-of-Treatment (EOT) visit[2]**	**Follow-up Period[3]**	
Treatment Cycles/Visits	1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[4]
Time of Visit	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[5]		± 3	± 3	± 3	± 3	+7	± 7	± 7

14. Patients with HBsAg (+) and/or HBcAb (+) should be further tested for hepatitis B virus (HBV) DNA titer; and HCV antibody positive subjects should be further tested for HCV RNA. In case of HBV DNA (-) and: 1) HBsAg (+), or 2) HBcAb (+) and HBsAg (-) at baseline, HBV antibody and HBV DNA should be tested every 2 cycles during the treatment period. In case of HCV antibody (+) and HCV RNA (-) at baseline, HCV antibody and HCV RNA should be tested every 2 cycles during the treatment period. If the test is done within 3 days before the first dose of investigational drug, it is not necessary to perform the test again.
15. PK and ADA sampling: PK and ADA samples for HLX10 or placebo will be collected at the following time points: within 3 days pre-dose in cycle 1 and thereafter every 4 cycles, at EOT visit and safety follow-up.
16. The tumor image used to determine disease progression can be used as the new baseline image for the post-PD treatment period if 1) the this is done within 28 days prior to receiving the first dose of HLX10 or placebo therapy and 2) there is no study treatment between the image and first dose of HLX10 or placebo therapy, otherwise a new baseline image must be performed prior to HLX10 or placebo treatment. Computerized tomography (CT) or magnetic resonance imaging (MRI) performed every 6 weeks (± 7 days) during the first 48 weeks after the start of study treatment, and every 9 weeks (± 7 days) after week 48 on sites including brain, chest, abdomen, pelvic cavity and any other sites suspected to have tumor lesions, in which brain MRI or CT (preferably MRI) and bone scans are performed in the treatment period as determined by the investigator according to clinical needs (if baseline brain CT/MRI shows that brain metastasis is not present, the subject should have follow up brain imaging only if clinically indicated at the discretion of the investigator. If baseline brain CT/MRI has confirmed central nervous system (CNS) metastasis, continuous brain imaging test should be carried out as part of the regular RECIST evaluation assessments); examination methods at the same site should be consistent as much as possible throughout the study; if there are no contraindications, contrast agent should be used. The investigator will assess the tumor images according to RECIST 1.1 (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation. At the EOT visit, if tumor imaging has been performed within the last 4 weeks, a re-test is not required. For subjects who discontinued for reasons other than disease progression, radiological assessments are to be continued as scheduled, until disease progression, initiation of new antineoplastic therapy, withdrawal of ICF, death, or end of study, whichever occurs first.

2 Introduction

2.1 Background

The global cancer statistics show that lung cancer is the most common cancer (11.6% of total cancer cases) and cause of death (18.4% of total cancer deaths) in the world. It is estimated that by 2018, 2.1 million new cases of lung cancer and 1.8 million new cases of lung cancer deaths will occur worldwide[1]. According to the data released by the National Cancer Center of China in 2018, there are about 781,000 new cases of lung cancer and 626,000 deaths from lung cancer each year in China, with the occurrence and mortality ranking first among malignant tumors[2].

Small cell lung cancer (SCLC) is derived from epithelial cells with neuroendocrine differentiation, accounting for 15%-20% of the total number of lung cancers[3]. The SCLC is staged using the United States (US) Veterans Administration staging system and is divided into a limited stage and an extensive stage. Most patients present with tumor metastases as the first symptom[4], and only 30% to 40% of patients are in the limited stage at the time of initial diagnosis[5]. Patients with extensive disease have shorter survival due to extensive tumor metastasis and poor physical status only with supportive care. The median survival time of untreated extensive small-cell lung cancer (ES-SCLC) is reported to be 2-4 months[6]. With a combination of surgery, radiotherapy and chemotherapy, the median survival of ES-SCLC patients can reach 8 to 13 months, with a 2-year survival rate of 5%[7].

Currently, systemic chemotherapy is still the primary treatment for ES-SCLC. The first-line platinum-based treatment recommended are the EP treatment (etoposide plus cisplatin), the EC treatment (etoposide plus carboplatin), the IP treatment (irinotecan plus cisplatin), and the IC treatment (irinotecan plus carboplatin). First-line treatment of SCLC is highly effective, but 80% of patients with limited-stage disease and almost all patients with extensive-stage disease relapse within one year, with a median survival of only 4 to 5 months after relapse[7]. Due to the limited understanding of SCLC genetic changes and the significant heterogeneity of SCLC at the genetic level, the success of some new treatment methods, such as intensive chemotherapy, supportive treatment, and molecular targeted therapy, did not benefit patients with extensive-stage SCLC. Therefore, there is an urgent need to explore more effective first-line treatments for extensive-stage SCLC.

Anti-PD-1 monoclonal antibodies have been approved for melanoma, non-small cell lung cancer (NSCLC), SCLC, head and neck squamous cell cancer, urothelial carcinoma, microsatellite instability-high or mismatch repair deficient solid tumors and colorectal cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma (HCC), Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, bladder cancer, primary mediastinal large B-cell

lymphoma and classical Hodgkin's lymphoma. Numerous clinical studies are ongoing with anti-PD-1 antibodies, either as monotherapy or in combination with various agents.

2.2 Study Rationale

With the deepening of the study on the molecular pathogenesis of cancer, the immunological mechanism of tumorigenesis and development has gradually become a study hotspot. It is becoming increasingly clear that cancer can be recognized by the immune system, and in some cases, the immune system can control or even eliminate tumors. PD-1 was originally cloned by Ishida et al.[8] as a member of the CD28 superfamily in murine T cell hybridomas. It is a monomeric glycoprotein that is mainly expressed on the surface of activated macrophages, T lymphocytes, B lymphocytes, natural killer (NK) cells, and some myeloid cells. Its ligands, PD-L1 (programmed death ligand 1) and PD-L2, are mainly expressed on tumor cells and antigen-presenting cells[9,10,11]. Because activation of the PD-1 gene may be involved in the classical type of programmed cell death, it is named programmed death receptor 1 (PD-L1). PD-L1 is highly expressed in a variety of cancers and is as high as 88% in some cancers. In these cancers (including lung cancer), PD-1 binds to PD-L1 in tumor tissues, weakens the body's immune response, protects tumor tissues from cytotoxic T cells, and leads to tumor immune tolerance[12,13]. Therefore, T cell anti-tumor response can be enhanced by blocking the binding of PD-1 to its ligand PD-L1[14,15,16,17,18].

In recent years, with the rapid development of tumor immunotherapy, the focus of first-line treatment for advanced NSCLC with no driver gene has gradually turned to immunotherapy, and multiple PD-1 inhibitors have been approved by the Food and Drug Administration (FDA) for NSCLC treatment; The National Comprehensive Cancer Network (NCCN) Guidelines have also included PD-1 inhibitors as one of the recommended protocols for the treatment of relapsed SCLC. In the absence of breakthrough of targeted drug treatment for SCLC in the past 30 years, a new drug has been discovered for SCLC. In 2018, the FDA approved Nivolumab for the treatment of relapsed SCLC. In addition, a number of clinical trials of PD-1 antibody combined with chemotherapy for SCLC are currently underway. Preliminary results show that PD-1 inhibitor plus chemotherapy can significantly improve overall survival and progression-free survival and is expected to become the new standard of first-line treatment for SCLC.

The survival of cytotoxic chemotherapy in patients with ES-SCLC reaches a plateau, leaving much room for improving the prognosis of such patients. Exposure of the immune system to high levels of tumor antigens can reasonably be expected to result in cytotoxicity effects on tumor cells by cytotoxic chemotherapy, and restoration of tumor-specific T cell immunity in this setting may produce deeper and durable responses than standard chemotherapy alone by inhibiting the PD-L1/PD-1 signaling pathway[19,20]. Therefore, it is reasonable to assume that the combination of

immunosuppressive and cytotoxic chemotherapy drugs may have a stronger synergistic anti-tumor effect.

Based on the considerable benefits of PD-1/PD-L1 inhibitors in patients with tumors, Shanghai Henlius Biotech, Inc. has developed an innovative monoclonal antibody HLX10 targeting PD-1. HLX10 is an IgG4-type humanized monoclonal antibody, where the gene sequence was obtained by screening using the hybridization technique and humanized modification was completed by genetic engineering, stable cell strains was constructed by using Chinese hamster ovary as a host cell, and the produced protein was connected to two identical heavy chains and two identical light chains by interchain disulfide bonds to form the “Y”-shaped typical human immunoglobulin IgG4 structure.

The available clinical data demonstrated that HLX10 is safe and tolerable in the phase I, first-in-human study in patients with advanced solid tumors, and in other clinical studies in patients with malignant solid tumors. And preliminary efficacy has been observed in some patients with advanced solid tumors in the first-in-human phase I clinical study (HLX10-001). The safety and efficacy of HLX10 will be further evaluated in clinical studies.

The platinum-based chemotherapy provided in this study is EC regimen (etoposide plus carboplatin), which is the first-line chemotherapy regimen for ES-SCLC recommended by NCCN and Chinese Expert Consensus on the Diagnosis and Treatment of Advanced Primary Lung Cancer (2016 Edition), allowing investigators and subjects to have more flexibility in conducting study and treatment according to the standard clinical practice of drugs.

Based on the results of preclinical and clinical studies, Shanghai Henlius Biotech, Inc. planned to conduct a phase III clinical study in previously untreated patients with ES-SCLC worldwide to compare the clinical efficacy and safety of HLX10 (recombinant anti-PD-1 humanized monoclonal antibody injection) in combination with chemotherapy (Carboplatin-Etoposide).

2.2.1 Preclinical Study of HLX10

***In vitro* pharmacodynamic studies of HLX10**

A series of *in vitro* pharmacodynamic studies of HLX10 versus the positive control nivolumab showed that: HLX10 can bind to the surface of activated T cells expressing PD-1 and has the ability to block the binding of PD-1 and PD-L1 or PD-L2 ligand on the cell surface. The binding and blocking ability of HLX10 showed dose-dependency. The analysis of *in vitro* mixed leukocyte reaction of HLX10 has shown that HLX10 can block the immunosuppression that is dependent on PD-1 and its ligand binding pathway, thereby stimulating activated $CD4^+$ T cells to

increase the T cell proliferative potential and produce more IL-2 cytokines. This phenomenon showed dose-dependency in both the study drug HLX10 and the positive control nivolumab.

In addition, to study the occupying ratio of HLX10 in PD-1 receptor on human T cells, different doses of HLX10 (50.0, 10.0, 2.0, 4.0×10^{-1}, 8.0×10^{-2}, 1.6×10^{-2}, 3.2×10^{-3} and 6.4×10^{-4} μg/mL) were pre-incubated in the whole blood of six healthy subjects to simulate the condition of HLX10 injected into human blood. The experiment results showed that; as the pre-incubated dose of HLX10 increased, the PD-1 receptor occupancy on $CD3^+$ T cells also increased. Out of the six healthy subjects, once the HLX10 concentration in the blood of four of the subjects reached 2 μg/mL, the PD-1 receptor occupancy on $CD3^+$ T cells would have reached above 80%.

***In vivo* pharmacodynamic studies of HLX10**

The results of the evaluation of anti-tumor effect and safety in the subcutaneous xenograft tumor model of HT-29 human colon cancer cell NOD/SCID immunodeficient mice showed that HLX10 did not cause adverse effects on the health and weight of the mice in each dose group, indicating that HLX10 is relatively safe. In terms of tumor inhibition, 30 mg/kg of HLX10 can effectively inhibit the growth of the subcutaneous xenograft tumor in HT-29 human colon cancer cell NOD/SCID immunodeficient mice in the presence of human peripheral blood mononuclear cells ($P<0.0001$).

The results of the evaluation of anti-tumor effect and safety in the subcutaneous xenograft tumor model of NCI-H292 human NSCLC cell NOD/SCID immunodeficient mice showed that HLX10 did not cause adverse effects on the health and weight of the mice at a higher dose, indicating that HLX10 is very safe. In terms of tumor inhibition, both the tumor volume observation and data statistics results in the HLX10 high-dose group versus the placebo group showed that 30 mg/kg of HLX10 had significant inhibitory effect on the growth of NCI-H292 tumor tissues in the presence of human peripheral blood mononuclear cells ($P<0.001$).

In the dose-finding trial (P16-106-TS), pharmacokinetic (PK) test (P16-106-YD), and long-term toxicity test (P16-106-CD) in *cynomolgus* monkeys; receptor occupancy (RO) at different time points was also investigated before and after intravenous injection of different doses of HLX10 to provide a basis for selection of the clinical effective dose and the initial dose.

Final results showed that the *in vivo* experiment result was consistent with the *in vitro* human peripheral blood PD-1 receptor occupancy (RO), i.e., once the HLX10 concentration in the blood of the subjects/experimental animals reached 2 μg/mL, the PD-1 receptor occupancy on $CD3^+$ T cells would have reached above 80%. In *cynomolgus* monkeys, when the blood concentration of two test animals in the 3 mg/kg group was below the lower detection limit (that is, 2 μg/mL), the

corresponding RO was still 79% and 97%, respectively. Combining all results, it was concluded that when a single dose of 3 mg/kg of HLX10 was given to *cynomolgus* monkeys, the RO saturation rate could be maintained for more than 4 weeks; when doses of 5 mg/kg were given to *cynomolgus* monkeys for 13 consecutive weeks (once a week), the RO saturation rate of 100% could still be achieved after the end of the recovery period of 6 weeks in some animals. It can thus be inferred that a relatively low dose of HLX10 (lower than 1mg/kg) in clinical practice can potentially achieve RO saturation, showing relatively good efficacy.

Tissue cross-reactivity of HLX10

The results of tissue cross-reactivity test of HLX10 in frozen normal human showed that HLX10-Biotin (2.0 μg/mL and 0.5 μg/mL) specifically binds to normal human lymphocytes from the lymph node, lung, ileum, stomach, spleen, fallopian tube, colon and thymus.

The results of tissue cross-reactivity test of HLX10 in *cynomolgus* monkeys showed that HLX10-Biotin (2.0 μg/mL and 0.5 μg/mL) specifically binds to normal *cynomolgus* monkey lymphocytes, including stomach, jejunum, colon, spleen, thymus and mesenteric lymph nodes.

General pharmacology study of HLX10

A general pharmacological evaluation of the central nervous system (CNS), cardiovascular system and respiratory system was conducted in *cynomolgus* monkeys, and this trial was a companion test of the long-term toxicity trial. During the trial, no test substance-related abnormalities were found in the clinical symptoms in each group of animals, and no obvious abnormalities were found in the activity and respiration of the animals. The abnormalities in a moribund female animal undergoing euthanasia on Day 55 in the high-dose group were found to be related to amoebic infection, and the abnormalities in a dead female animal on Day 64 were found to be related to the allergic reaction induced by drug administration. No toxicologically-significant regular changes in body temperature, systolic blood pressure, diastolic blood pressure, mean arterial pressure, oxygen saturation, heart rate, P-R interval, Q-T interval, QTc interval, QRS duration and other ECG parameters were found in surviving animals. Therefore, intravenous infusion of 5, 50 and 100 mg/kg of HLX10 once a week in *cynomolgus* monkeys for 13 consecutive weeks had no significant effects on the CNS, cardiovascular system and respiratory system of *cynomolgus* monkeys.

Acute toxicity test of HLX10

A dose-finding toxicity test of repeated intravenous infusion of HLX10 was conducted in *cynomolgus* monkeys for 4 weeks, and they were given intravenous infusion of 5 mg/kg, 50 mg/kg and 100 mg/kg of HLX10. The drug was administered on Day 1, Day 8, Day 15 and Day22, and all animals were euthanized on Day 29. Gross anatomy was performed for

observation. No animals died or were moribund during the trial. One male animal in the medium-dose group developed loose stools and soft stools on Day 15-20 and Day 21-29 respectively. One female animal in the medium-dose group also developed loose stools on Day 11-13, Day 15-20 and Day 29, which were considered to be possibly related to the test substance (male and female animal findings). No test substance-related abnormalities were observed in the clinical observations of animals in the low-dose group and the high-dose group. No dosing-related abnormal changes in body weight, food intake, body temperature, electrocardiography (ECG) parameters, coagulation parameters, blood biochemistry or gross anatomic observation were observed in the animals of each dose group. 4/4, 3/4 and 4/4 animals in the 5, 50 and 100 mg/kg groups tested positive for anti-drug antibodies/neutralizing antibodies (ADA/NAb) respectively. The first occurrence of ADA/NAb was on Day 8, and the antibody titer range was <1-128. Based on the results of this trial, after HLX10 was given to *cynomolgus* monkeys for 4 weeks, the animals could tolerate 100 mg/kg of HLX10 very well. The dose of 100 mg/kg can be used for longer-term repeat-dose trials.

Long-term toxicity test of HLX10

A toxicity and toxicokinetic trial of repeated intravenous infusion of HLX10 for 13 weeks followed by a 6-week recovery period was conducted in *cynomolgus* monkeys, in which placebo and 5, 50 and 100 mg/kg of HLX10 were given once a week for 13 consecutive weeks. No test substance-related deaths or moribund animals were found in the low- and medium-dose groups during the trial. At the dose of 100 mg/kg, one female animal died of drug-related allergic reaction and another moribund female animal was euthanized on Day 55 due to amoebic infection. Loose stools and/or soft stools were observed in each dose group. Of which, female animals in the high-dose group (100 mg/kg) had a slightly higher incidence with slightly longer duration. The gastrointestinal symptoms described above were possibly related to drug administration, which was consistent with the reported adverse reactions of PD-1 monoclonal antibody. With the exception of the two deaths in the high-dose group, the gastrointestinal reactions of the remaining animals (loose stools/soft stools) were completely recovered after the 6-week recovery period. No other test substance-related abnormalities were observed in the surviving animals of the dose group during the trial. With the exception of the female animal in the high-dose group that was euthanized on Day 55, all animals in the dose groups tested positive for ADA/NAb, and the ADA/NAb response was the highest in the low-dose group. The antibody titer also increased as the number of doses increased, and it lasted until the end of the recovery period (Day 134). In combination with toxicokinetic (TK) results, the occurrence of ADA/NAb significantly reduced systemic exposure in all dose groups. After repeated intravenous infusion of 5 and 50 mg/kg of HLX10 in *cynomolgus* monkeys once a week for 13 consecutive weeks, no significant toxicity was observed, and no reactions were observed at the site of drug

administration. There were no significant effects on the major functional systems such as the cardiovascular system, CNS or respiratory system. Under the conditions of this trial, the maximum no observed adverse effect level (NOAEL) of HLX10 was 50 mg/kg. The AUC_{last} and maximum (or peak) serum concentration (C_{max}) in male animals were 597.60 h*mg/mL and 4,909.72 μg/mL respectively, and the AUC_{last} and C_{max} in female animals were 403.64 h*mg/mL and 3,726.17 μg/mL respectively at this dose on Day 85.

Preclinical pharmacokinetics study of HLX10

The results of the PK study in *cynomolgus* monkeys receiving a single intravenous infusion of HLX10 showed that after intravenous infusion of HLX10 at 3, 10 and 30 mg/kg, the serum drug concentration increased with the increase in dose. The systemic exposure (C_{max} and AUC_{last}) increased with the increase in dose. The mean retention time (MRT) was between 153.02-231.28 h. The elimination half-life ($t_{1/2}$) was between 137.97-256.99 h. The results showed that the test substance generally showed linear PK characteristics in *cynomolgus* monkeys in the dose range of 3-30 mg/kg. The clearance rate and volume of distribution (Vz) of HLX10 were similar in all dose groups, and they were between 0.13-0.23 mL/h/kg and 38.05-53.52 mL/kg. All animals in the 3, 10 and 30 mg/kg HLX10 dose groups tested positive for ADA/NAb on Day 8, Day 15, Day 22 and Day 29. The first occurrence of ADA/NAb was on Day 8, and the antibody titer range was between <1-512. Other than the statistical difference ($P<0.05$) in the 10 mg/kg group where in the area under the concentration-time curve (AUC_{last} and AUC_{inf}) for female animals was lower than that for male animals, there were no statistically significant differences in the PK parameters between genders in other dose groups. Analysis of the impact of ADA/NAb status on PK showed that 2/3 of female animals in the 10 mg/kg group produced relatively strong antibodies on D22 with an antibody titer of 8-128, resulting in a slightly faster elimination in female animals than male animals and a smaller area under the curve (AUClast and AUCinf).

Toxicokinetic study of HLX10

A toxicokinetic study was performed along with the dose-finding toxicity test of repeated intravenous infusion of HLX10 in *cynomolgus* monkeys for 4 weeks. The results showed that: on Day 1 and Day 22, the systemic exposure of HLX10 (C_{max} and AUC_{last}) increased with the increase in dose. On Day 22, the production of anti-drug antibodies in some animals resulted in a faster elimination of serum HLX10 concentration. In ADA-negative animals, the mean values of C_{max} and AUC_{last} in each dose group were higher on Day 22 than on Day 1, indicating that there was accumulation of the drug to some extent. This characteristic was also shown in the serum HLX10 concentration in pre-dose samples on Day 22. The accumulation factor was between 2.24-2.41. Compared to Day 1, the volume of distribution of HLX10 decreased and the clearance rate decreased in the ADA-negative group on Day 22. In the ADA-positive group, the clearance rate increased significantly.

Another toxicokinetic study was performed along with the toxicity and toxicokinetic trial of repeated intravenous infusion of HLX10 for 13 weeks followed by a 6-week recovery period in *cynomolgus* monkeys. The results showed that, on Day 1 and Day 85, the systemic exposure of HLX10 (C_{max} and AUC_{last}) increased with an increase in dose, showing dose-dependent toxicokinetic characteristics. Some animals produced ADA after repeated dosing. In ADA-negative animals, the mean values of C_{max} and AUC_{last} in each dose group were higher on Day 85 than on Day 1, indicating that there was accumulation of the drug. This characteristic was also shown in the serum HLX10 concentration in pre-dose samples on Day 85. The accumulation factor was between 2.34-4.32. Compared to Day 1, the volume of distribution of HLX10 decreased and the clearance rate decreased in the ADA-negative group on Day 85. In the ADA-positive group, the clearance rate increased significantly. On Day 1, the systemic exposure (AUC_{last} and AUC_{inf}) was slightly higher in male animals than in female animals and the clearance rate was slightly lower in male animals than in female animals in the 100 mg/kg dose group, but there were no significant differences in PK parameters between genders on Day 1 and Day 85 in the remaining animals.

Immunogenicity and immunotoxicity of HLX10

An evaluation test of immunogenicity and immunotoxicity were carried out in *cynomolgus* monkeys, and this trial was a companion test of the long-term toxicity trial. The results showed that, after repeated intravenous infusion of 5, 50 and 100 mg/kg of HLX10 in *cynomolgus* monkeys once a week for 13 consecutive weeks, no immunotoxicity was observed at doses of 5 and 50 mg/kg. At the dose of 100 mg/kg, one female animal died of an allergic reaction, the ADA was positive, and IL-6 increased after dosing. At the dose of 100 mg/kg, the ratios of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ of male animals decreased, and the increase in $CD8^+$ was related to the pharmacologic effects of the test substance. Anti-drug antibodies were found after HLX10 dosing in the animals, and the incidence of ADA in the low-dose group was higher than that in the medium- and high-dose groups. Antibody titer increased with an increase in duration of drug administration and may result in a significant decrease in systemic exposure. HLX10 is a humanized antibody and is an exogenous substance to *cynomolgus* monkeys. Hence, the production of immunogenicity is a reasonable phenomenon in the animals. The evaluation of immunogenicity of antibody drugs is suitable in human clinical trials.

Genetic Toxicology Studies

The genotoxicity isn’t required to be evaluated for monoclonal antibodies like HLX10 according to ICHS6 (R1).

Other preclinical studies of HLX10

The results of the hemolytic study of HLX10 showed that HLX10 with a concentration of 10 mg/mL had no hemolytic effect on human erythrocytes *in vitro* and did not cause erythrocyte coagulation.

Local irritability study was conducted along with the long-term toxicity test, and the results showed that after repeated intravenous infusion of 5, 50 and 100 mg/kg of HLX10 in *cynomolgus* monkeys once a week for 13 weeks, there was no significant irritative damage to local blood vessels and surrounding tissues within the concentration range of 0.5-10.0 mg/mL.

2.2.2 Clinical Study of HLX10

To date, HLX10 has been administered to human subjects in 14 ongoing clinical studies. Clinical studies of HLX10, given as monotherapy or in combination with chemotherapy or other antibodies (anti-VEGF antibody HLX04), are being conducted in patients with advanced solid tumors, previously untreated metastatic non-squamous NSCLC, previously treated unresectable or metastatic MSI-high or mismatch repair deficiency solid tumors, previously treated advanced HCC, gastric cancer, metastatic esophageal squamous cell carcinoma (ESCC), metastatic colorectal cancer (mCRC), relapsed and/or advanced cervical cancer, and advanced head and neck cancer.

The clinical efficacy and safety results from these studies, as well as the nonclinical toxicology and safety data, provide evidence to support continued clinical development for HLX10.

2.3 Benefit/Risk Assessment

2.3.1 Potential benefits

Available clinical data for HLX10 include that collected from clinical studies of HLX10, which was given as monotherapy and/or in combination with chemotherapy or other antibody (anti-VEGF antibody HLX04), in patients with advanced solid tumors, previously untreated metastatic non-squamous NSCLC, previously treated unresectable or metastatic MSI-H or dMMR solid tumors, previously treated advanced HCC, gastric cancer, metastatic ESCC, mCRC, relapsed and/or advanced cervical cancer, and advanced head and neck cancer.

The available clinical data shows that HLX10 monotherapy or combined with other therapies was safe and tolerable in patients with malignant tumors.

Only 1 subject in the 3 mg/kg dose cohort (n=6) experienced DLT during the first cycle in the HLX10 first-in-human phase I study in patients with advanced solid tumors with four dose levels

(0.3, 1, 3 and 10 mg/kg). The maximum tolerated dose (MTD) was not reached until 10 mg/kg of HLX10 was given every two weeks. Accumulation of HLX10 was observed following multiple dose administration. The 0.3 mg/kg of HLX10 was enough to saturate the PD-1 binding and induce the functional blockade. The efficacy results demonstrated anti-tumor activity of HLX10 in this first-in-human phase I study with DCR of 68.8%, ORR of 6.3%, and median PFS of 107.0 days.

In the phase II study of HLX10 in patients with previously treated HCC, 1 subject in the dose level A (n=7) of safety run-in stage experienced DLT (increased total bilirubin is 39.4 μmol/L which is >2 mg/dL and considered to be caused by hepatocellular cancer progression).

The study showed the anti-tumor activity of HLX10 and patients with advanced solid tumors can benefit from HLX10.

2.3.2 Identified and potential risks

PD-1/PD-L1 inhibitors not only enhance the anti-tumor effect of cellular immunity, but could also enhance the normal immune response, leading to immune tolerance imbalance and immune-related adverse reactions (irAEs). Immune-related adverse reactions can affect any organ in the human body, and nearly two-thirds of patients currently treated with immune checkpoint inhibitors experience irAEs of varying degrees[19,20]. In February 2018, NCCN and American Society of Clinical Oncology (ASCO) jointly issued the Guidelines for the Management of Toxicity Related to Immunotherapy (Version 1, 2018), which states that the immune-related AEs of the skin, intestine, endocrine, lung and musculoskeletal systems are relatively common, while the immune-related AEs of the cardiovascular, hematological, renal, neurological and ophthalmic systems are rare. Most immune-related AEs were mild-moderate in severity; common irAEs known in patients currently treated with PD-1/PD-L1 inhibitors were as follows: skin toxicity (mainly maculopapular rash and pruritus; 30% to 40%), diarrhea and/or colitis (8% to 19%), fatigue (16% to 24%), immune-related hepatitis (5%), hypothyroidism (4% to 10%), hyperthyroidism (4%), hypophysitis (< 1%), type 1 diabetes, immune-related pneumonia, sarcoidosis, inflammatory arthritis, etc. Others such as cardiovascular AEs, anemia, thrombocytopenia, nephritis, encephalopathy, leukoencephalopathy, post-reversible encephalopathy syndrome, peripheral motor and sensory neuropathy, uveitis, episcleritis, blepharitis, and acute pancreatitis occurred less frequently.

HLX10 is currently being studied with limited safety information available. The available clinical data from the first-in-human phase I clinical study (HLX10-001), shows that the most frequently reported study drug related adverse events were nausea, fatigue and decreased appetite, constipation, vomiting and pyrexia. The severity was mainly grade 1-2. The most

frequently reported serious adverse event (SAE) that was greater or equal than grade 3 was pyrexia.

In another phase I clinical study (HLX10HLX04-001) of the study drug combined with another antibody, no DLT was observed in the 18 subjects when the study drug was administered from 1 mg/kg to 10 mg/kg.

In the phase II study (HLX10-008-HCC201) of HLX10 in patients with previously treated HCC, 1 subject received HLX10 (3 mg/kg) combined with HLX04 (5 mg/kg) once every 2 weeks experienced DLT at safety run in stage (increased total bilirubin is 39.4 μmol/L which is >2 mg/dL and considered to be caused by hepatocellular cancer progression).

In the ongoing phase III study (HLX10-002-NSCLC301) of HLX10 in patients with previously untreated non-squamous non-small cell lung cancer (NSCLC), 6 subjects have received HLX10 (4.5 mg/kg) + HLX04 (15 mg/kg) + carboplatin (AUC=5) + pemetrexed (500 mg/m^2) once every 3 weeks with no major safety concerns. No grade ≥4 hematologic toxicity and grade ≥3 non-hematologic toxicity-safety events and grade ≥2 pneumonia (and no recovery to grade 1 in 3 days) occurred after the treatment of the first cycles. No serious adverse drug reactions (ADRs) were observed in the first stage of the study (safety run-in period). The most common ADRs included platelet count decreased, white blood cell count decreased, neutrophil count decreased and hypertriglyceridaemia.

Several other phase II and III clinical studies of the study drug are ongoing, where HLX10 has been administered as monotherapy and/or in combination with chemotherapy or other antibody, in patients with advanced solid tumors, previously untreated metastatic NSCLC and previously treated unresectable or metastatic MSI-H (microsatellite instability-high) or dMMR (deficiency in mismatch repair) solid tumors. The available clinical data showed that the study drug given as a monotherapy or combined with other therapies was safe and tolerable in patients with malignant tumors.

The most commonly reported side effects with probability greater than 5% include: rash, pyrexia, anemia, diarrhea, nausea, decreased appetite, platelet count decreased, white blood cell count decreased, neutrophil count decreased, nephritis, hepatic function abnormal, and hypothyroidism.

Adverse events related to the study drug reported in these studies which are serious, fatal and life-threatening include: pyrexia, myocarditis, platelet count decreased, neutrophil count decreased, white blood cell count decreased, pneumonitis, hepatic function abnormal, colitis, pancreatitis, and renal impairment.

More detailed information about the known and expected risks of HLX10 can be referred to in the Investigator's Brochure.

2.3.3 Overall benefits: risk and ethical assessment

At present, chemotherapy for advanced SCLC has encountered the bottleneck of efficacy, and there is an urgency to explore to explore more effective first-line treatment for SCLC. With the progress of various studies, immune checkpoint combination therapy has become a new treatment option for SCLC, which is likely to greatly improve the prognosis of SCLC patients. At the same time, the AEs of the atezolizumab combination protocol were consistent with the known toxicity of monotherapy, and no new safety signals were found. Based on the current study data of HLX10, only 2 subjects experienced DLTs (1 subject received HLX10 monotherapy [3 mg/kg] once every 2 weeks, and 1 subject received HLX10 [3 mg/kg] combined with HLX04 [5 mg/kg] once every 2 weeks), the MTD was not reached yet. The available safety data and PK data demonstrated that the safety of HLX10 in patients is acceptable and adequate to support the implementation of this phase III clinical study.

3 Objectives and Endpoints

Objectives	Endpoints
Primary To compare the clinical efficacy of HLX10 in combination with chemotherapy versus placebo in combination with chemotherapy in previously untreated patients with ES-SCLC.	Primary Efficacy Endpoint • Overall survival (OS) Secondary Efficacy Endpoints • Progression-free survival (PFS) (assessed by the independent radiology review committee [IRRC] based on Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) • PFS (assessed by the investigator based on RECIST 1.1 and a modified RECIST 1.1 for immune-based therapeutics [termed iRECIST]) • PFS2 (assessed by the investigator based on RECIST 1.1) • Objective response rate (ORR) (assessed by the IRRC and investigator based on RECIST 1.1) • Duration of response (DOR) (assessed by the IRRC and the investigator based on RECIST 1.1)
Secondary To compare the safety and tolerability of HLX10 in combination with chemotherapy versus placebo in combination with chemotherapy in previously untreated patients with ES-SCLC. To measure the exposure following HLX10 administration.	Safety Endpoints • Adverse events (AEs) (including serious adverse events [SAEs]), laboratory tests (routine blood test, blood chemistry, coagulation function, urinalysis, myocardial function and thyroid function), 12-lead electrocardiogram (12-lead ECG), vital signs, and physical examination, etc. PK Endpoint • Concentration of HLX10 in serum Immunogenicity Endpoint • HLX10 anti-drug antibody (ADA) positive rate Biomarker Endpoint • Relationship between PD-L1 expression, microsatellite instability (MSI), tumor mutation burden (TMB) in tumor tissue and efficacy. Quality of life assessment

4 Study Design

4.1 Overall Design

This is a randomized, double-blind, placebo-controlled, multicenter, clinical phase III study to compare the clinical efficacy, safety and tolerability of recombinant humanized anti-PD-1 monoclonal antibody injection (HLX10) or placebo in combination with chemotherapy in patients with previously untreated ES-SCLC, to collect PK parameters and to investigate the biomarker related to efficacy. See Section 1.2 for study schema and Section 1.3 for SoA.

Subjects in this study will be randomized to arm A or B at 2:1 ratio as follows:

- Arm A (HLX10): HLX10 + chemotherapy (carboplatin-etoposide)
- Arm B (control): placebo + chemotherapy (carboplatin-etoposide)

Randomization is stratified by PD-L1 expression level (negative: tumor proportion scores [TPS] <1%, positive: TPS ≥1%, or not evaluable/not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years).

After screening, subjects meeting the inclusion criteria and none of the exclusion criteria will be enrolled. Included subjects will be treated with HLX10 or placebo in combination with chemotherapy once every 3 weeks, until disease progression, death, intolerable toxicity, withdrawal of informed consent, or occurrence of other reasons specified in the protocol (whichever occurs first).

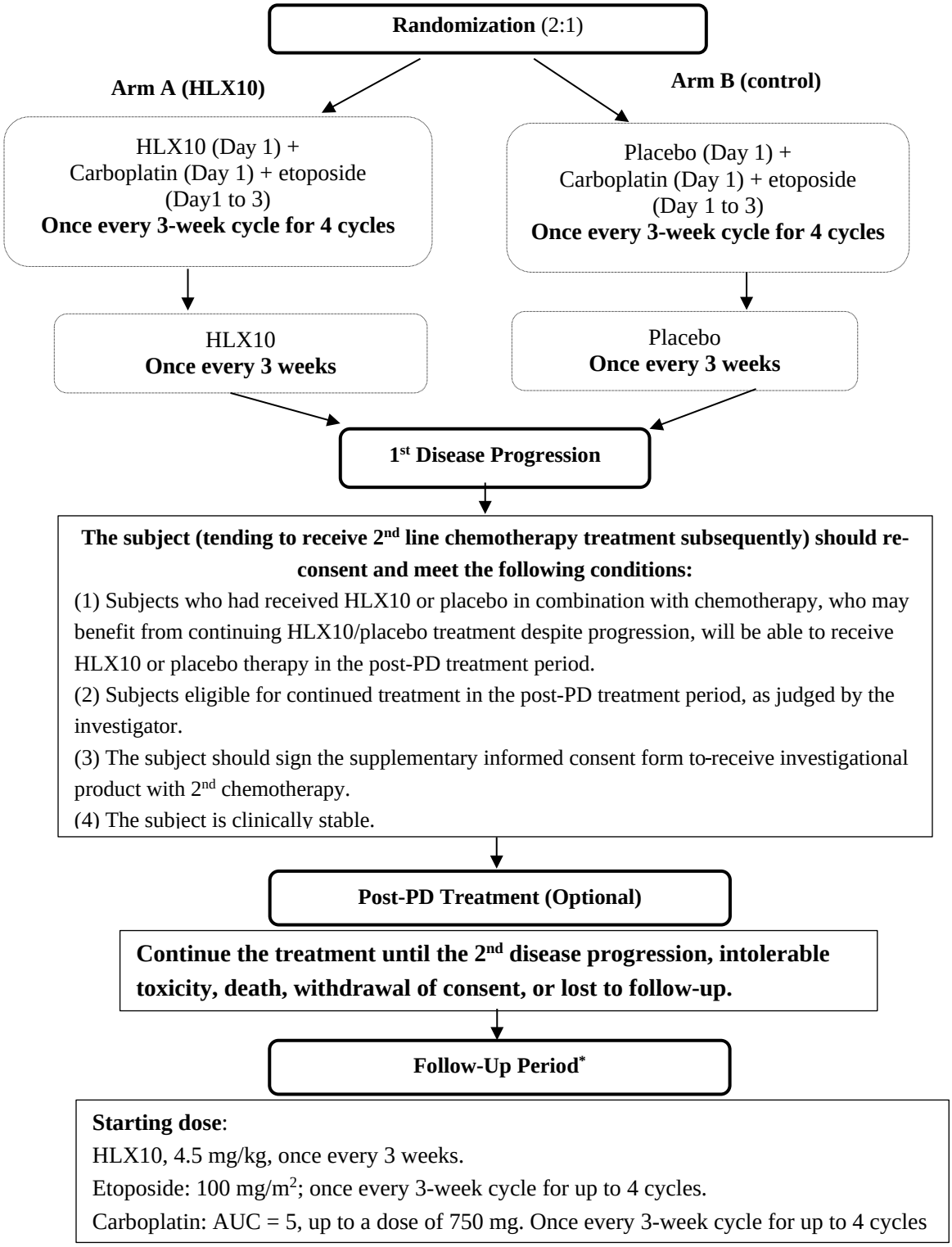
Initial treatment should be discontinued when they have evidence of disease progression as assessed per RECIST 1.1. If a subject has 1st disease progression and is clinically stable, and tends to receive 2nd line chemotherapy treatment subsequently (the selection of 2nd line chemotherapy may refer to the NCCN guidelines or the ESMO guidelines), it is at the discretion of the investigator to continue treating the subject with blinded HLX10 or placebo assignment per protocol in addition to the 2nd line chemotherapy, until the 2nd disease progression, intolerable toxicity, death, withdrawal of consent, or lost to follow-up. Subjects who permanently discontinue initial treatment due to an adverse event, withdrawal of consent, or for any reason other than disease progression, will not be eligible for the post-PD treatment.

Subjects who **meet the following conditions** may continue the treatment after appropriate discussion with the subject and obtaining the supplementary informed consent.

1. Subjects who had received HLX10 or placebo in combination with chemotherapy, who may benefit from continuing HLX10/placebo treatment despite progression, will be able to receive HLX10 or placebo therapy in the post-PD treatment.
2. Subjects eligible for continued treatment in the post-PD treatment period, as judged by the investigator.
3. The subject should sign the supplementary informed consent form to receive investigational product with 2nd line chemotherapy.
4. The subject is clinically stable, defined as:
    a) With no clinical signs and/or symptoms (including worsening of laboratory findings) that might indicate disease progression.
    b) A stable Eastern Cooperative Oncology Group (ECOG) performance status score.
    c) No rapid disease progression or tumor progression requiring urgent alternative medical intervention at critical anatomical sites (e.g., spinal cord compression).

The primary endpoint of this study is to compare the OS of HLX10 in combination with chemotherapy versus placebo in combination with chemotherapy.

Figure 1: Schematic of study treatment



* Follow-Up Period includes safety follow-up and survival follow-up. Patients who are not eligible for post-PD treatment will be followed up for safety and survival status.

4.2 Scientific Rationale for Study Design

Rationale for Control Drug Selection

The platinum-based chemotherapy provided in this study is EC regimen (etoposide plus carboplatin), which is the first-line chemotherapy regimen for ES-SCLC recommended by NCCN and Chinese Expert Consensus on the Diagnosis and Treatment of Advanced Primary Lung Cancer (2016 Edition), allowing investigators and subjects to have more flexibility in conducting study and treatment according to the standard clinical practice of drugs.

Basis for Combination Therapy

With more insight on the molecular pathogenesis of cancer, the immunological mechanism of tumorigenesis and development has gradually become a study hotspot. It is becoming increasingly clear that cancer can be recognized by the immune system, and in some cases, the immune system can control or even eliminate tumors. PD-1 was originally cloned by Ishida et al.[8] as a member of the CD28 superfamily in murine T cell hybridomas. It is a monomeric glycoprotein that is mainly expressed on the surface of activated macrophages, T lymphocytes, B lymphocytes, NK cells, and some myeloid cells. Its ligands, PD-L1 (programmed death ligand 1) and PD-L2, are mainly expressed on tumor cells and antigen-presenting cells[9,10,11]. Because activation of the PD-1 gene may be involved in the classical type of programmed cell death, it is named programmed death ligand 1 (PD-L1). PD-L1 is highly expressed in a variety of cancers and is as high as 88% in some cancers. In these cancers (including lung cancer), PD-1 binds to PD-L1 in tumor tissues, weakens the body's immune response, protects tumor tissues from cytotoxic T cells, and leads to tumor immune tolerance[12,13]. Therefore, T cell anti-tumor response can be enhanced by blocking the binding of PD-1 to its ligand PD-L1[14,15,16,17,18].

In recent years, with the rapid development of tumor immunotherapy, the focus of first-line treatment for advanced NSCLC with no driver gene has gradually turned to immunotherapy, and multiple PD-1 inhibitors have been approved by the FDA for NSCLC treatment; The NCCN Guidelines have also included PD-1 inhibitors as one of the recommended protocols for the treatment of relapsed SCLC. In the absence of breakthrough of targeted drug treatment for SCLC in the past 30 years, a new drug has been discovered for SCLC. In 2018, the FDA approved Nivolumab for the treatment of relapsed SCLC. In addition, a number of clinical trials of PD-1 antibody combined with chemotherapy for SCLC are currently underway. Preliminary results show that PD-1 inhibitor plus chemotherapy can significantly improve overall survival and progression-free survival and is expected to become the new standard of first-line treatment for SCLC.

The survival of cytotoxic chemotherapy in patients with ES-SCLC reaches a plateau, leaving much room for improving the prognosis of such patients. Exposure of the immune system to high levels of tumor antigens can reasonably be expected to result in cytotoxicity effects on tumor cell (TC) by cytotoxic chemotherapy, and restoration of tumor-specific T cell immunity in this setting may produce deeper and durable responses than standard chemotherapy alone by inhibiting the PD-L1/PD-1 signaling pathway[19,20]. Therefore, it is reasonable to assume that the combination of immunosuppressive and cytotoxic chemotherapy drugs may have a stronger synergistic anti-tumor effect.

Rationale for Post-PD Treatment

Patients with ES-SCLC experience rapid tumor growth, fast clinical deterioration, and have an overall poor prognosis. First-line therapy with a platinum agent and etoposide has consistently demonstrated high response rates and significant clinical benefit. However, considering the limited availability and efficacy or greater toxicity of treatment options after withdrawal, and for better adaptation to standard clinical practice, subjects may be considered for subsequent treatment assignment blinded beyond radiographic disease progression per RECIST 1.1, at the discretion of the investigator, after appropriate discussion with the patient and obtaining informed consent.

In addition, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because disease progression (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Related research shows that shorter treatment increases the risk of relapse or progression, and there are potential benefits to patients receiving longer IO (Immunotherapy) treatment[21]. Because of the potential for pseudoprogression/tumor-immune infiltration, this study will allow patients to remain on treatment after apparent radiographic disease progression per RECIST 1.1, provided all criteria meet post-PD treatment conditions.

4.3 Justification for Dose

Based on the results of the preclinical and clinical trials of HLX10, the currently available PK and ADA data support HLX10 4.5 mg/kg based on mean body weight, administered every 21 days as the recommended dose for phase III clinical study. Results of Dose Exposure Response analysis demonstrated both 4.5 mg/kg every three weeks and 3.0 mg/kg every two weeks were oversaturated doses. Given the fact that no MTD was observed in anti-PD-1 antibodies and the European Medicines Agency (EMA) and FDA approved oversaturated doses for nivolumab (nivo) and pembrolizumab (pembro) in clinical practice across multiple tumor types, Henlius believes that 4.5 mg/kg every three weeks or 3.0 mg/kg every two weeks is justified and safe.

See Sections 2.2.1 and 2.2.2 for details.

4.4 End of Study Definition

The end of the study, defined as the final analysis of OS, will be performed when a target number of OS events (approximately 342) are observed, and for final analysis the α is 0.046 (two-sided) based on the O'Brien-Fleming alpha spending function.

Or

The end of the study is defined as the date when all subjects enrolled completed the safety follow-up 90 days after the end of treatment visit.

Whichever occurs last. Additionally, the sponsor may decide to terminate the study at any time.

4.5 Unblinding

Emergency Unblinding

During study drug treatment, if a life-threatening condition determined by the investigator to be related to the use of the study drug, or if the investigator considers the knowledge of the subject's drug is helpful for management of the adverse event, emergency unblinding may be used. The decision to unblind in emergency situations shall be the responsibility of the investigator, and the sponsor will not delay or reject it. However, the investigator may contact the sponsor or its designated personnel to discuss the unblinding and the most favorable option for the subject. The investigator should ensure that emergency unblinding is performed only during events stipulated in the protocol. The investigator should immediately notify the sponsor of the emergency unblinding and the reason for the unblinding, and record these clearly on the subject's source documents. The unblinding process will be completed on Interactive Web/Voice Response System (IWRS/IVRS) using the emergency unblinding personal identification number. Unblinding can only occur in an affected subject if unblinding is required.

5 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

The study population will consist of participants with ES-SCLC. Participants must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Voluntary participation in clinical studies; fully understand, be informed about the study and have signed the informed consent form (ICF); willingness to follow and ability to complete all trial procedures.
2. Male or female aged ≥ 18 years at the time of signing the ICF.
3. Histologically or cytologically diagnosed with ES-SCLC (according to the Veterans Administration Lung Study Group staging system).
4. No prior systemic therapy for ES-SCLC (including systemic chemotherapy, molecular targeted therapy, biological therapy, and other investigational therapies, etc.).
5. Patients who have received chemoradiotherapy for previous limited stage SCLC must be treated with curative intent and have a treatment-free interval of at least 6 months from the last course of chemotherapy, radiotherapy, or chemoradiotherapy to the diagnosis of extensive stage SCLC.
6. At least one measurable lesion as assessed by the IRRC according to RECIST 1.1 within 4 weeks prior to randomization.

   Note: Measurable lesions are not from previously irradiated sites. If the lesion at the previously irradiated site is the only selectable target lesion, a radiological assessment showing significant progression of the irradiated lesion should be provided by the investigator.
7. Patients must provide tumor tissues that meet the requirements for the determination of PD-L1 expression levels. Patients are assessed for an evaluable PD-L1 expression category (negative: TPS <1%, positive: TPS ≥1%, or not evaluable/not available) by the central laboratory for randomization.

   Note: It is recommended to provide formalin-fixed tumor tissue samples, paraffin-embedded tumor specimens (preferred), formalin-fixed paraffin-embedded (FFPE), tumor specimens or newly prepared unstained serial tissue sections (preferably adhesive slides) within 6 months prior to the first dose of study medication. A relevant pathology report must also be provided for the above specimens. Freshly collected specimens, radical resections, core needle biopsy, excisions, incisions, punch or clamp biopsies are acceptable (newly obtained tissues are preferred). Fine-needle aspirations (i.e., samples that lack a complete tissue structure and provide only cell suspension and/or cell smear), brush biopsies, and cell pellet samples from pleural or peritoneal effusions are unacceptable. For detailed requirements for tissue samples, see the laboratory manual.

8. Prior antineoplastic therapy must have been ≥ 2 weeks from the first dose in this study with treatment-related AEs resolved to NCI-CTCAE Grade ≤ 1 (except for Grade 2 alopecia).
9. An ECOG PS score of 0 or 1.
10. An expected survival ≥ 12 weeks.
11. Subjects with prior denosumab use that can and agree to switch to bisphosphonate therapy for bone metastases starting prior to randomization and throughout treatment.
12. Normal major organ functions as defined by the following criteria (no blood transfusions, or treatment with albumin, recombinant human thrombopoietin or colony-stimulating factor within 14 days prior to the first dose in this study):

Hematologic system	
Absolute neutrophil count (ANC)	≥ 1.5×10^9/L
Lymphocyte	≥ 0.5×10^9/L
Platelet (PLT)	≥ 100×10^9/L
Hemoglobin (Hb)	≥ 90 g/L
Hepatic functions	
Total bilirubin (TB)	≤ 1.5×upper limit of normal (ULN) For patients with Gilbert's syndrome, total bilirubin ≤ 3 × ULN is acceptable
Alanine transaminase (ALT)	≤ 2.5×ULN; ≤ 5 × ULN for patients with liver metastases
Aspartic transaminase (AST)	≤ 2.5×ULN; ≤ 5 × ULN for patients with liver metastases
Alkaline phosphatase (ALP)	≤ 2.5×ULN; ≤ 5.0 × ULN for patients with liver or bone metastases
Renal functions	
Creatinine (Cr)	≤ 1.5×ULN; In case of > 1.5 × ULN, creatinine clearance ≥ 50 mL/min (calculated from Cockcroft-Gault formula)

Coagulation functions	
Activated partial prothrombin time (APTT)	≤ 1.5×ULN
Prothrombin time (PT) or International normalized ratio (INR)	≤ 1.5×ULN
The above requirements apply only to subjects who are not receiving anticoagulant therapy; subjects who are receiving anticoagulant therapy must maintain a stable dose of anticoagulants.	

13. Female patients must meet one of the following conditions:
    a. Menopause (defined as no menses for at least 1 year and no confirmed cause other than menopause), or
    b. Surgically sterilized (removal of the ovaries and/or uterus), or
    c. Of child-bearing potential, but must meet the following:

    - Serum pregnancy test must be negative within 7 days prior to randomization, and
    - Agree to use birth control methods with an annual failure rate of <1% or maintain abstinence (avoid heterosexual intercourse) (from the signing of ICF to at least 6 months after the final dose of study drug) (birth control methods with an annual failure rate of <1% include bilateral tubal ligation, male sterilization, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine contraceptive devices and copper-containing intrauterine contraceptive devices or condoms), and
    - Must not be breast-feeding.

14. Male patients must: agree to abstinence (avoid heterosexual intercourse) or take contraception measures as follows: male patients with a pregnant partner or a partner of childbearing potential must remain abstinent or use a condom to prevent embryonic exposure during study treatment and for at least 6 months after the last dose of study drug. Periodic abstinence (e.g., contraceptive methods based on calendar day, ovulation, basal body temperature or post-ovulation) and external ejaculation are ineligible methods of contraception.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Histologically or cytologically confirmed mixed SCLC.
2. Other active malignancies within 5 years or at the same time. Localized tumors that have been cured, such as basal cell carcinoma, squamous-cell skin cancer, superficial bladder

cancer, prostate carcinoma in situ, cervical cancer in situ and breast cancer in situ are acceptable.

3. Patients who are preparing for or have received an organ or bone marrow transplant.
4. Pleural or pericardial effusion requiring clinical intervention, or ascites.
5. Patients with known or documented active CNS metastases and/or carcinomatous meningitis at screening. However, the following subjects are allowed to be enrolled: 1) Subjects with asymptomatic brain metastases (i.e., no progressive central nervous system symptoms caused by brain metastases, no requirement for corticosteroids, and lesion size ≤ 1.5 cm) may be included, but are required to receive regular brain imaging as a site of lesion. 2) Subjects with treated brain metastases which have been stable for at least 2 months (as confirmed by 2 radiological examinations at least 4 weeks apart after treatment of brain metastases), with no evidence of new or enlarging brain metastases, and with discontinued steroids 3 days prior to study drug administration. (Stable brain metastases here should be confirmed before the first dose of the study drug.).
6. Subjects with spinal cord compression that has not been radically treated with surgery and/or radiotherapy.
7. Patients with myocardial infarction within half a year before the first dose of the study drug, poorly controlled arrhythmia (including QTc intervals ≥ 450 ms for males and ≥ 470 ms for females) (QTc intervals are calculated by Fridericia's formula).
8. Class III to IV cardiac insufficiency according to NYHA classification or a left ventricular ejection fraction < 50% by cardiac color Doppler.
9. Subject has uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium > ULN).
10. Subject with peripheral neuropathy ≥ Grade 2 by CTCAE.
11. Human immunodeficiency virus (HIV) infection, positive test for HIV antibody.
12. Active or latent pulmonary tuberculosis.
13. Subjects with previous and concurrent interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonitis and severe impaired pulmonary function that may interfere with the detection and management of suspected drug-related pulmonary toxicity, as judged by the investigator.
14. Hepatitis B (positive test for HBsAg or HBcAb and positive test for HBV-DNA) or Hepatitis C (positive tests for HCV antibody and HCV-RNA). Hepatitis B and C co-infection (positive test for HBsAg or HBcAb and positive test for HCV antibody).
15. Known active or suspected autoimmune diseases. Subjects in a stable state with no need for systemic immunosuppressant therapy are allowed to enroll.
16. Treatment with live vaccines and all COVID-19 vaccines (fully administered to the

required number of doses) within 28 days prior to study drug administration; inactivated viral vaccines for seasonal influenza are allowed.

17. Subjects requiring treatment with systemic corticosteroids (> 10 mg/day prednisone efficacy dose) or other immunosuppressive drugs within 14 days prior to the first dose or during the study. However, in the absence of active autoimmune disease, subjects are allowed to use topical or inhaled steroids and adrenal hormone replacement therapy at doses equivalent to ≤ 10 mg/day of prednisone efficacy.
18. Any active infection requiring systemic anti-infective therapy within 14 days prior to study drug administration or subjects with a positive RT-PCR test for SARS-CoV-2 infection at randomization. Subjects with a history of COVID-19 infection must have a negative RT-PCR test prior to the first dose of the study drug.
19. Major surgery within 28 days prior to the first dose of the study drug, defined as: surgeries requiring at least 3 weeks of recovery to be able to receive treatment in this study.
20. Radical radiation therapy within 3 months prior to study medications.

Note: Palliative radiotherapy to bone or palliative radiotherapy to superficial lesions is allowed according to local standards 14 days prior to the first dose. Radiotherapy covering more than 30% of the bone marrow area within 28 days prior to the first dose is not allowed.

21. The subject has previously received other antibodies/drugs against immune checkpoints, such as PD-1, PD-L1, CTLA4, etc.
22. Participation in any other ongoing clinical studies, or less than 14 days from the end of the previous clinical study treatment to the start of this trial.
23. Known history of severe allergy to any monoclonal antibody.
24. Known hypersensitivity to carboplatin or etoposide.
25. Pregnant or lactating women.
26. Known history of psychotropics abuse or drug abuse.
27. In the judgment of the investigator, the subject has any other factors that may lead to a premature discontinuation.

5.3 Lifestyle Considerations

No restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to

ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. In this study, one re-screening is allowed for ineligible subjects: in case of unqualified laboratory tests, one re-test can be performed within the screening time window, without giving a new screening number; for other conditions noncompliant with the inclusion/exclusion criteria, subjects should be re-screened with a new screening number.

6 Study Drug

Study drug is defined as any investigational interventions, marketed products, or placebo intended to be administered to a study subject according to the study protocol.

Investigational product is defined as HLX10/placebo.

Study drugs will be administered IV.

6.1 Study Interventions Administered

HLX10

Name	Recombinant anti-PD-1 humanized monoclonal antibody injection (HLX10)
Formulations	Liquid
Specifications	100 mg (10 mL)/vial
Storage conditions	2-8°C
Manufacturer	Shanghai Henlius Biopharmaceuticals Co., Ltd
Drug supplier	Shanghai Henlius Biotech, Inc.

Placebo

Injection that is not externally recognizable and contains no HLX10 active ingredient, manufactured by Shanghai Henlius Biopharmaceuticals Co., Ltd, and provided by Shanghai Henlius Biotech, Inc.

Chemotherapy Drug

Commercially available carboplatin and etoposide consolidated and provided by Shanghai Henlius Biotech, Inc. For information regarding the formulation, preparation, storage, and dosing information, please refer to currently-approved information on prescription of carboplatin and etoposide.

6.2 Dosing Regimen Preparation/Handling/Storage/Accountability

Dosing Regimen and Preparation

Study drugs are administered as follows, each treatment cycle is 3-weeks (every 21 days).

Investigational/reference product:

- **HLX10**: 4.5 mg/kg, IV infusion for 30 to 90 minutes, administered on Day 1 of each cycle, once every 3 weeks (21 days).
- **Placebo:** IV infusion, administered on Day 1 of each cycle, once every 3 weeks (21 days).

The infusion of investigational product is completed between 30 mins and 90 mins if there is not any infusion reaction. The diluted drug solution is recommended to be used within 6 hours of preparation and has been shown to be stable for up at 24 hours. The diluted drug solution needs to be stored at approximately 2-8 °C for no longer than 24 hours and be kept from light if not used within 6 hours.

Other study drugs: chemotherapy

- Etoposide: 100 mg/m^2, IV infusion, on Days 1, 2, and 3 of each cycle. On Day 1, etoposide shall be administered following infusion of carboplatin.
- Carboplatin: AUC = 5, up to a dose of 750 mg, IV infusion, on Day 1 of each cycle.

  Dose of carboplatin shall be calculated according to the following Calvert formula:

  - Dose of carboplatin (mg) = target AUC x [(CrCl (mL/min) + 25)]
  - Creatinine clearance (CrCl) is calculated according to the Cockroft-Gault formula (Appendix 6: Cockcroft and Gault Formula) on the basis of the subject's most recent serum creatinine and body weight. Note: If CrCl calculated by the Cockroft-Gault formula is > 125 mL/min, CrCl shall be calculated using an alternative formula in accordance to the standards of the study site, or capped at 125 mL/min.

A combination of HLX10 or placebo + carboplatin + etoposide shall be administered in a 3-week treatment cycle; carboplatin and etoposide are administered for a maximum of 4 cycles.

Refer to Figure 1 "Schematic of study treatment" for the regimen of each treatment arm. In each 3-week cycle, the subjects shall receive an IV infusion of HLX10 or placebo, followed by intravenous infusion of carboplatin, then etoposide on the first day of dosing with close monitoring of vital signs. Administration of HLX10/placebo shall be blinded, while carboplatin + etoposide are openly administered. Subjects will continue to receive etoposide on Days 2 and 3. The treatment will continue until disease progression, intolerable toxicity, discontinuation

decided by the subject or the investigator, death, withdrawal of informed consent, pregnancy, noncompliance with protocol or procedure requirements, administrative reasons, or other reasons specified in the protocol, whichever occurs first. The dosing window is ±3 days from the scheduled date of administration (from the date of the first dose). Drugs administered outside the dosing window is considered a delayed dose, and subsequent doses shall be administered according to the actual date of last administration. If chemotherapy is not used due to toxicity or other reasons in a certain cycle, it is not counted as the number of combined chemotherapy cycles. After completing 4 cycles of chemotherapy, even if the subject does not meet the above criteria, the chemotherapy will not be continued.

Handling, Storage, Management, and Distribution

The study drug will be dispatched by the sponsor or a third-party designated by the sponsor. The study sites should establish a good drug receipt procedure and require a specialized personnel to receive the study drug and sign the drug receipt form. The study drug can only be used in the trial specified by this protocol and only authorized staff will be able to access these drugs.

The study site should establish a strict drug management system with a specialized personnel responsible for the safekeeping and distribution of the study drug and establish a registration system. The study site should ensure that the storage conditions of the study drug are in compliance with the requirements and are recorded and stored.

Only the study personnel or his/her designee will be able to provide the drug to the subjects and manage the drug. The dispensing and returning of each drug should be recorded on the specialized record sheet in a timely manner. If the study drug is lost, dispersed, or misused, it should be recorded in detail.

The study drug will be returned and destroyed by the sponsor or the third-party designated by the sponsor, and must not be released into the market.

Refer to the drug management and operating procedure for detailed operation.

Packaging and labeling

Vials of HLX10/placebo, carboplatin, and etoposide are labeled by a third-party designated by the sponsor.

The content of the label includes: drug name, drug number, protocol number, specifications, dosage and administration, batch number, expiration date, storage requirements, and other specific information required by the local regulatory authority and Good Manufacturing Practice.

6.3 Measures to Minimize Bias: Randomization and Blinding

All subjects will be centrally randomized the IWRS/IVRS. Each subject will be assigned a unique number (randomization number) that encodes the subject's assignment to one of the two arms of the study, according to the randomization schedule generated by Medidata using a validated computer program. Details of the procedure are described in the IWRS/IVRS Manual provided to all sites.

Randomization

This study adopts a randomized, double-blind study design. The eligible subjects will be randomly assigned to the following two groups using the IWRS/IVRS at 2:1 ratio:

- Arm A (HLX10): HLX10 + chemotherapy (carboplatin-etoposide)
- Arm B (control): placebo + chemotherapy (carboplatin-etoposide)

Stratification factors for randomization include: PD-L1 expression level (negative: TPS <1%, positive: TPS ≥1%, or not evaluable/not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years).

Blinding

The blinding will be performed by the Statistical Unit during study treatment. The subjects, investigator, sponsor, and designated personnel will not be aware of the randomization and treatment allocation. This study will perform overall unblinding after the last subject completes the end of study visit. Unblinding will be performed only in case of emergency (emergency rescue can only be conducted if the type of randomized drug received by the subject is known) or as required by regulatory authorities. Otherwise, blinding should be maintained. All randomization numbers will be unblinded only after all data are entered into the database, all data queries are resolved, and subjects are included in analysis sets.

6.4 Study Treatment Compliance

During the study and during the follow-up period, the situation of drug use during the study treatment will be recorded in the eCRF. Any deviations from the medications stipulated in the study protocol will be recorded in the eCRF, including the date and reason for the use of medication. The clinical research associate (CRA) will review treatment compliance during the study site visits and at the end of the study.

6.5 Concomitant Therapy

The investigator may, at his/her discretion, administer any drugs that he/she deems necessary for the treatment of subjects and are not expected to interfere with the evaluation of the study drugs (i.e., the best supportive care). Prophylactic and other supportive treatment for nausea and vomiting may be given to subjects according to local medical practice before and after carboplatin and etoposide administration.

All concomitant medications (including start/end dates, total daily doses, and indications) must be documented in the subject's source document and in the corresponding section in the eCRF.

6.5.1 Prohibited Concomitant Therapies

Medications or treatments prohibited during the study treatment period include:

- Any other systemic chemotherapy, radiotherapy, immunotherapy, biological therapy, molecular targeted therapy with anti-tumor effects or modern Chinese medicine preparations in anti-tumor therapy approved for marketing by National Medical Products Administration (NMPA) (see Appendix 9) during initial treatment period, immunomodulators with adjuvant anti-tumor effects (e.g., thymosin, lentinan, interleukin-12, etc.) that has anti-tumor effect; local remission of an isolated lesion (other than the target lesion) is acceptable (e.g., local surgery or radiotherapy for bone metastasis)
- Any other clinical trial drugs;
- Other immunosuppressive drugs, including but not limited to: systemic glucocorticoids with a dose of more than 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor (TNF)-inhibitors. Except for the following situations:
    - The use of immunosuppressive drugs to treat study treatment-related AEs;
    - Where they are used for short-term prophylaxis in subjects who are expected to receive chemotherapy, and the use of glucocorticoids in subjects who have hypersensitivity reactions required by the prescription information on the drug;
    - Used in subjects allergic to contrast agents;
    - The use of inhaled, topical, and intranasal glucocorticoids is permitted;
    - If clinical indications are present and the investigator considers it necessary to carry out disease management for the subject, the use of short-term glucocorticoids (e.g., to control chronic obstructive pulmonary disease, radiotherapy, nausea, etc.) is permitted;

- Live vaccine administration within 4 weeks prior to the first dose of study drug and during the study. Live vaccines include but are not limited to: measles, epidemic parotitis, rubella, varicella, yellow fever, rabies, Bacillus Calmette-Guerin, typhoid fever vaccines. Injectable inactivated seasonal influenza vaccines are allowed, but intranasal live attenuated influenza vaccines are not allowed.

6.5.2 Permitted Medications/Treatments

Medications and therapies which are permitted during the study include:

- Treatment for complications, AEs or symptoms (including blood products, blood transfusions, infusions, antibiotics, anti-diarrheal medications, etc.), with the exception of medications/therapies which are expected to interfere (or interact) with the evaluation of the study;
- Antiemetics;
- Nutritional support;
- Medication or therapy necessary for previous disease.

6.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or his/her qualified designee will review all new anti-cancer therapy initiated after the discontinuation of trial treatment. If the subject continues the post-PD treatment, he/she must choose to receive 2nd line chemotherapy. The preferred 2nd line chemotherapy was determined by the investigators following the NCCN /or ESMO guidelines and communicated as such to the subjects who chose to continue the post-PD treatment. Any other anti-PD1 and anti-PD-L1 therapy are not allowed.

6.6 Dose Modification

Starting from the beginning of HLX10 or placebo infusion, subjects shall be closely monitored for allergic reactions that may occur within a few minutes. In case of mild symptoms (such as flushing or local skin reactions), drugs may be administered at a slower speed. For serious hypotension, bronchospasm, or generalized rash/erythema, the administration should be stopped immediately, and appropriate therapies should be given. For a life-threatening reaction, including allergic reactions, hypersensitivity reactions, renal failure, severe cardiopulmonary events, and severe skin reactions, etc., the medications shall be discontinued permanently.

The dosing window is ± 3 days from the scheduled date of administration (from the date of the first dose). Drugs administered outside the dosing window is considered a delayed dose, and subsequent doses shall be administered according to the actual date of last administration. During the course of combined treatment, if a delay of more than 2 weeks is expected due to the toxicity

of chemotherapy, only HLX10 or placebo will be administered until the toxicity returns to the standard of chemotherapy administration. Chemotherapy may be continuously suspended for a maximum of 6 weeks, otherwise the chemotherapy should be discontinued. If a delay of more than 2 weeks is expected due to the toxicity of HLX10 or placebo, only chemotherapy will be administered until the toxicity recovers to the HLX10 or placebo dosing criteria. HLX10 or placebo therapy may be continuously suspended for a maximum of 12 weeks, otherwise the HLX10 or placebo will be discontinued. In case of a delay due to toxicity with equivocal association, all the study drugs shall be synchronously delayed if the event is expected to return to re-dosing standards within 2 weeks.

General principles for dose modification

Any modified or delayed doses or adopted supportive therapies should be recorded in the source documents and eCRFs. Adverse events are assessed for severity according to CTCAE v5.0.

- For concomitant conditions already present at baseline, dose modifications may be determined by the investigator based on changes in severity of toxicity. For example, if the subject already has a Grade 1 weakness at baseline, and the severity increases to Grade 2 during treatment, it may be considered to make dose modification according to Grade 1 toxicity due to 1-grade increase in toxicity.
- If multiple toxicities of different severities occur at the same time, the dose should be adjusted according to the most severe toxicity.
- If the toxicity is related to one of the study drugs only (for example, HLX10, carboplatin or etoposide) as assessed by the investigator, dose modification of that study drug only with reference to the corresponding dose modification principle is acceptable, and the subject can continue receiving the other study treatment in the absence of other contraindications.
- If the toxicity is associated with only one of the chemotherapy medications as assessed by the investigator, the dose of the other chemotherapy medication may not be adjusted.
- In the event that a delay is required for reasons of toxicity (not definitively related to which drug), similar delays of all study drugs at the same time are required if recovery to a re-dosing level is expected within 2 weeks.
- If HLX10/placebo, carboplatin, or etoposide is interrupted due to toxicity, study treatment must be restarted, keeping HLX10/placebo in sync with the chemotherapy treatment cycles.

Principles for HLX10 or placebo dose modifications

In the event of HLX10- or placebo-related toxicity, a delay in HLX10 or placebo is allowed rather than dose adjustment. Subjects who miss a scheduled infusion should be actively contacted to arrange another visit as soon as possible for administration. Administration of HLX10 or placebo may be delayed, but a dosing interval of up to 12 weeks is considered intolerable of HLX10/placebo where HLX10 or placebo will be permanently discontinued, and the subject should withdraw from the trial. For a treatment delay due to intolerance to HLX10 or placebo, chemotherapy should be administered as scheduled, and HLX10 or placebo may be postponed to the next cycle with no more than 12 weeks between doses.

Principles for chemotherapy dose modifications

In the event of intolerance to etoposide/carboplatin, doses may be adjusted twice in accordance with the prescribing information of carboplatin and etoposide, the investigator's decision based on the subject's safety, and local treatment standard practice. Once reduced, the dose cannot be increased back to 100%.

If treatment is delayed due to intolerance to chemotherapy, chemotherapy may be delayed to the next cycle of administration, with the maximum permissible interval for chemotherapy not exceeding 6 weeks.

The following are **recommended carboplatin dose modifications for hematological and non-hematological toxicities**.

Hematological toxicities

At the start of each cycle, ANC must be $\geq 1.5 \times 10^9$/L and PLT count must be $\geq 100 \times 10^9$/L. Otherwise the treatment should be postponed for up to 42 days to provide a sufficient period for recovery. According to the guidelines of the ASCO and NCCN, growth factors can be given to subjects with reduced ANC and/or PLT. At the beginning of subsequent cycles after recovery, dosage shall be adjusted based on the PLT and ANC nadirs of the last cycle (refer to Table 1).

Table 1: Carboplatin Dose Modifications for Hematological Toxicities

Toxicity[a]	**Dose of carboplatin**
ANC < 0.5 $\times 10^9$/L and PLT ≥ 50 $\times 10^9$/L	75% of the planned dose
PLT < 50 $\times 10^9$/L, regardless of ANC	75% of the planned dose
PLT < 50 $\times 10^9$/L with Grade 2 hemorrhage, regardless of ANC	50% of the planned dose
ANC < 1$\times 10^9$/L with fever ≥ 38.5 °C	75% of the planned dose

ANC = Absolute neutrophil count, PLT = Platelets.

[a]Nadir of the last cycle

Doses shall be permanently reduced at the first onset of neutropenic fever or thrombocytopenia (PLT < 25 × 10^9/L or < 50 × 10^9/L with signs of bleeding or need for blood transfusion). For the need for dose reduction at the second onset of neutropenic fever or thrombocytopenia, dose of carboplatin shall be reduced in accordance with the physician's judgement and local standard medical practices. In case of neutropenic fever or Grade 4 neutropenia, colony-stimulating factors (such as granulocyte colony-stimulating factor) may be administered in place of reduced doses in accordance with local standard medical practices and ASCO guidelines. For subjects who require a third dose reduction, the chemotherapy shall be discontinued immediately.

Subjects who require dosing modification due to both ANC and platelet count shall receive a lower dose.

Treatments may be postponed for up to 42 days until the first day when ANC is ≥ 1.5 × 10^9/ L and PLT is ≥ 100 × 10^9/L. However, if the counts fail to recover within 3 weeks, the chemotherapy shall be reduced or suspended in accordance with the physician's judgement and local standard medical practices before ANC recovery.

The investigator shall pay attention and remain alert to early and significant signs of myelosuppression, infections and neutropenic fever, to ensure a prompt and appropriate management of such complications. The investigator shall remind the subjects of the signs of such complications and encourage them to seek medical attention as soon as possible.

If chemotherapy is to be suspended due to hematological toxicities, a complete blood count (including white blood cell (WBC) differential counts) shall be performed once a week until such counts return to the lower limit specified for the treatment. The treatment shall be completed as planned thereafter.

No dose reduction is required for anemia. Subjects shall be given supportive care in accordance with the guidelines of the institution where the attending physician is located.

Non-hematological toxicities

In the event of non-hematologic toxicities, treatment shall be delayed for up to 6 weeks until the measurement falls below or is equivalent to the subject's baseline value (or Grade ≤1 if the patient did not have the toxicity at baseline). At the beginning of the subsequent cycles, the dose shall be reduced based on the dose of the last cycle leading to non-hematologic toxicities. The following table includes related recommendations for dosing modifications for non-hematological toxicities.

Table 2: Carboplatin Dose Modifications Based on Non-Hematological Toxicities in Previous Treatments

Toxicities		**Modified carboplatin dose by % of planned dose[a]**
Diarrhea	Grade 3 or 4[b]	75%
Nausea/vomiting	Grade 3 or 4[c]	75%
Neurotoxicity	Grade 2	75%
	Grade 3 or 4	50% or permanent discontinuation
Transaminitis	Grade 3	75%
	Grade 4	Discontinuation
Others	Grade 3 or 4	75%

AUC = Area under the concentration-time curve.

[a] Modify carboplatin dose to a specific percentage of the previous AUC, if deemed appropriate by the attending physician

[b] Grade 3 or 4 diarrhea requiring adequate antidiarrheal medication or any severity of diarrhea that requires hospitalization.

[c] Despite the use of anti-emetics.

Recommended etoposide dosing modifications are as follows. The investigator may adhere to the following or to his/her clinical practice during the study.

Table 3: Etoposide Dose Modification for Subjects with Renal Impairment

Creatinine clearance rate (mL/min)	**Dose of etoposide**
>50	100%
15–50	75% of the dose

Modification of etoposide dose based on the prescribing information for etoposide and the local medical standard is permitted. Once reduced, the current dose will never return to 100%.

6.7 Intervention after the End of the Study

Subjects will receive standard of care treatment as determined by their healthcare provider after completion of the study.

7 Discontinuation of Study Intervention, Participant Discontinuation, and Study Termination

7.1 Discontinuation of Study Intervention

7.1.1 Reasons for Premature Discontinuation

A discontinuation of treatment means that the subject will no longer receive a study medication of this trial. Reasons for the discontinuation of treatment may include:

1. Poor subject compliance that has affected the efficacy and safety evaluation;
2. The occurrence of AEs or SAEs in the subjects, who are deemed unsuitable to continue receiving the study drug treatment as judged by the investigator;
3. Evidence of clear disease progression or worsening of the disease;
4. A delayed study drug administration meeting the criteria specified in the protocol;
5. Subject lost to follow-up or death during treatment;
6. Subject decides to withdraw informed consent;
7. Subject decides to discontinue treatment;
8. Other reasons of discontinuation as determined by the investigator in the best interest of the subject.

7.1.2 Management of premature discontinuations

The reasons for premature discontinuations shall be documented in the eCRF by the investigator.

All subjects who discontinue the trial prematurely (except patients who withdraw informed consent) and agree to continued follow-up of associated clinical outcome information, shall undergo an EOT visit and be followed up for safety and survival. See Section 8.2.4 for assessments during the follow-up period.

Subjects who discontinue the trial for reasons other than disease progression and agree to continue follow-up of associated clinical outcome information should be radiologically followed up until disease progression, withdrawal of informed consent, death or start of a new antineoplastic therapy.

All AEs present at the time of discontinuation must be followed up until the outcomes of such AEs.

In case of an enrolled subject's withdrawal for any reason, no subject replacement is permitted.

7.2 Participant Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

If a subject develops fever or symptoms suspected of being a result of COVID-19 during the study, they will be instructed to follow-up with their regular healthcare provider or follow the instructions for suspected COVID-19 cases per their local health authority. A subject will discontinue treatment based on discussion with the Sponsor and Medical Monitor under the following circumstances: any suspected or confirmed COVID-19 case will be immediately discontinued from study treatment for up to 12 weeks after the last study drug administration; subjects who recover from the infection within 12 weeks from the last study drug administration, can continue treatment following Sponsor’s confirmation.

Refer to Section 1.3, the SoA, for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3 Loss of Participants to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible (and within the visit window, where one is defined) and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, three telephone calls and, if necessary, a certified letter to the subject’s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject’s medical record/CRF.

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.4 Premature Termination of Study and Site Closure

The study may be terminated prematurely for the reasons described below, and the premature termination of the study must be approved in writing by both the principal investigator and the Sponsor, and the results of the study should be reported as required by the protocol.

1. The study is unlikely to be completed within an acceptable time frame due to difficult enrollment of subjects;
2. The investigator doubts the safety of the drug during the study, and believes that continuing the study will bring serious risks to the subjects;
3. The principal investigator and the Sponsor believe that it is necessary to terminate the study prematurely based on the number of AEs and their severity;
4. The expected efficacy cannot be reached, and it is not necessary to continue the clinical study;
5. Withdrawal of the study by the drug regulatory authority;
6. The Sponsor has the right to decide to terminate the study in a study site if the following occurs:
    - Serious violation of International Conference on Harmonization Good Clinical Practice (ICH-GCP) by the study site
    - Multiple serious protocol violations by the study site

After termination of the study, all study-related records should be retained for reference.

8 Study Assessments and Procedures

8.1 Tests and Evaluations during the Study

See Section 1.3 for SoA of tests and evaluations during the study.

Demographics and Medical History

Demographics contain information on date of birth, gender, ethnicity, etc.

At screening, lung cancer history of subjects must be collected, including: clinical phase, pathological diagnosis, diagnosis method, diagnosis date and prior medications (surgical history, radiotherapy/chemotherapy history, etc.). Subjects' personal histories are also collected, including allergy history, drug dependence history, smoking and drinking; in addition, histories of other important diseases within one year prior to signing the informed consent form must be collected.

Prior Treatment and Concomitant Treatment

All prior and concomitant medications are recorded from 30 days prior to signing the informed consent through the safety follow-up visit should be recorded. Concomitant medications associated with AEs are recorded up to 90 days after the last study treatment. Prior and concomitant medications (including traditional Chinese medicine) are collected and recorded in the eCRF.

Adverse Event Assessment

All AEs and treatment emergent AEs are recorded from the time of signing the ICF until 90 days after the last study treatment. If a subject started a new antineoplastic therapy during the AE collection period, only information on AEs related to study treatment are collected after the new antineoplastic therapy.

Quality of Life Assessment

In this study, subjects will be assessed for quality of life, including by EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-LC13.

EQ-5D-5L: The EQ-5D is a standardized measure of health status developed by the EuroQol group that allows a simple and general rating of health status from a clinical and economic evaluation perspective. The scale is applicable to a variety of health conditions and treatments. It lists simple descriptive features, gives single index values for health state, and can be used for clinical and economic evaluation of health treatments as well as population health surveys. This questionnaire contains 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect an increased degree of severity.

Since 2009, the EuroQol group has developed a more sensitive EQ-5D version (EQ-5D-5L) in which the range of responses for each dimension is expanded, i.e., from three levels of increasing severity to five. Preliminary studies have shown that, compared to the nature of the 3-level version of the measured parameters, the 5-level version improved in the following aspects: reduced ceiling effects, increased robustness, and enhanced ability to distinguish between different health levels.

During the study, subjects are asked to select the most appropriate level from the five dimensions described above, indicating their current health status. The questionnaire also includes a visual analog scale in which subjects will be asked to rate their current health state on a scale from 0 to 100, with 0 indicating the worst health state (see Appendix 3: Quality of Life Scale EORTC QLQ-C30, EQ-5D-5L, EORTC QLQ-LC13).

EORTC QLQ-C30: The EORTC QLQ-C30 v3 questionnaire is an established measure of health-related quality of life (HRQoL) and is commonly used as an endpoint in oncology clinical trials. The questionnaire assesses HRQoL/health status through 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, nausea and vomiting), and 1 global health and QoL (quality of life) scale. The 6 individual symptom measures include: dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties (see Appendix 3: Quality of Life Scale EORTC QLQ-C30, EQ-5D-5L, EORTC QLQ-LC13). For the 15 domains described above, the total score is standardized to a range from 0 to 100, where higher scores indicate stronger functioning, higher HRQoL or higher symptom levels.

EORTC QLQ-LC13: The QLQ-LC13 is a 13-item self-administered questionnaire for lung cancer disease that will be used along with the EORTC QLQ-C30. The scale includes both multiple and single lung cancer-related symptom parameters (i.e., cough, hemoptysis, dyspnea and pain), as well as side effects of conventional chemotherapy and radiotherapy (i.e., alopecia, neurological disorders, oral pain and dysphagia). Similar to the EORTC QLQ-C30, all questions (except one) are on a 4-point scale: "not at all", "a little", "quite a bit", and "very much". Only 1 question (43rd question "Did you take any medicine for pain?") is with response options of "yes" or "no". The QLQ-LC13 are scored similarly to the EORTC QLQ-C30.

Echocardiogram

Echocardiography must be performed for all subjects at screening, and the results of left ventricular ejection fraction are recorded.

During the study treatment, if the subject has clinical symptoms such as shortness of breath, tachycardia, cough, jugular vein distention and hepatomegaly, relevant examinations must be timely performed after assessed by the investigator.

12-Lead Electrocardiogram (ECG)

Subjects will rest for 5 minutes before each 12-lead ECG. In case of clinically significant ECG abnormalities at a visit, a re-examination is recommended within 24 hours.

Complete Physical Examination

At screening, the subjects shall have a complete physical examination including head and neck (including thyroid gland), chest (including heart and lung), abdomen (liver, gallbladder, spleen and kidney), limbs, skin, lymph nodes, nervous system as well as the general conditions of subjects, with the examination results recorded; special attention should be paid to the symptoms and signs in respiratory system.

Symptom-Directed Physical Examination

A symptom-directed physical examination will be performed by the investigator during study treatment based on clinical observations and symptoms. Clinically significant physical examination abnormalities that are judged by the investigator to be significantly worse than the screening period or newly developed should be recorded as AEs.

Height, Body Weight and Vital Signs

Height is measured only at screening.

Vital signs should be assessed after the subject has rested for at least 5 minutes, including blood pressure (mmHg), pulse (beats/min), respiratory rate (breaths/min) and body temperature (°C), and body weight should be recorded.

Body weight and vital signs are to be measured prior to each dose during study treatment. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose of investigational product, the dose of investigational product must be recalculated. All doses should be rounded to the nearest milligram.

ECOG Score

Evaluation of ECOG performance status by the investigator is recommended throughout the study. The first ECOG score should be completed within 7 days prior to randomization.

Local Laboratory Tests

Local laboratory tests performed at study sites include routine blood test, serum biochemistry, coagulation, myocardial function, urinalysis, thyroid function, virology, tuberculosis screening (as requested by the Bulgarian Drug Agency for Bulgarian subjects) and pregnancy test. Routine blood test, biochemistry, coagulation, myocardial function and urinalysis should be performed within 3 days pre-dose in each treatment cycle; For laboratory tests from the screening period completed on Day -7 ~ Day -1, it is not necessary to repeat the test again before the first administration (C1D1). For chemotherapy, routine blood tests should be performed on Day 8 (± 3 days) of each treatment cycle to closely monitor bone marrow suppression. For aforementioned laboratory tests scheduled on the same day as study treatment, the study treatment can be arranged only after the test results are obtained. During the treatment period, thyroid function and blood pregnancy (for females of childbearing age only) tests are performed 3 days pre-dose every 2 cycles.

Table 4: Laboratory Tests

Routine blood test	**Biochemistry**	**Urinalysis[a]**	**Others**
Red blood cell count (RBC) Hemoglobin (HGB) Platelet (PLT) White blood cell count (WBC) White blood cell differential count and percentage • Basophils (BAS&BAS%) • Eosinophils (EOS&EOS%) • Lymphocytes (LYM&LYM%) • Monocytes (MON&MONO%) • Neutrophils (NEU&NEUT%)	Urea (UREA)/Blood urea nitrogen (BUN) Creatinine (CR) Fasting blood glucose (GLU) Total bilirubin (TB) Direct bilirubin (TB) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Total cholesterol (CHOL) Total protein (TP) Albumin (ALB) Sodium (Na) Potassium (K) Magnesium (Mg) Chloride (Cl) Calcium (Ca) Phosphorus (P)	Specific gravity (SG) Urine leukocytes Urine pH value Urine protein (U-PRO) Urinary glucose (U-GLU) Ketones (KET) Urine occult blood (BLO) Microscopic examination of white blood cells (U-WBC) Microscopic examination of red blood cells (U-RBC)	**Coagulation function** Prothrombin Time（PT） Activated Partial Thromboplastin Time (APTT) International Normalized Ratio (INR) **Myocardial function** Troponin-I (TnI)/troponin-T (TnT), creatine kinase isoenzyme (CK-MB)/creatine kinase (CK), myoglobin Brain Natriuretic Peptide (BNP)/N-terminal pro-Brain Natriuretic Peptide (NT-pro BNP) **Thyroid function tests[b]** Triiodothyronine (T3 or FT3) Thyroxine (T4 or FT4) Thyroid-stimulating hormone (TSH) **Virology[c]** Hepatitis B Surface Antigen (HBsAg) Anti-HBs (HBsAb) Anti-HBc (HBcAb) Anti-Hepatitis C (HCV) Antibody HBV DNA (optional) HCV RNA (optional) Anti-HIV

Routine blood test	Biochemistry	Urinalysis[a]	Others
			Pregnancy test[d]
			Tuberculosis test[e]

a. If a subject has two consecutive 2++ urine protein or one ≥ 3+++, urine protein should be tested at 24 hours;

   Microscopic examination of white blood cells (U-WBC) should be collected if urine leukocytes is out of normal range. Microscopic examination of red blood cells (U-RBC) should be collected if urine occult blood is out of normal range.

b. Thyroid function tests will be performed during screening and within 3 days prior to drug administration every 2 treatment cycles during the treatment period;

c. All subjects are tested for HBsAg or HCV antibody at screening; Patients with HBsAg (+) and/or HBcAb (+) should be further tested for HBV DNA titer; and HCV antibody positive subjects should be further tested for HCV RNA. In case of HBV DNA (-) and: 1) HBsAg (+), or 2) HBcAb (+) and HBsAg (-) at baseline, HBV antibody and HBV DNA should be tested every 2 cycles during the treatment period. In case of HCV antibody (+) and HCV RNA (-) at baseline, HCV antibody and HCV RNA should be tested every 2 cycles during the treatment period.

d. Women of childbearing potential should have a blood pregnancy test within 7 days prior to randomization and must have a negative result for enrollment; this is also tested within 3 days pre-dose every 2 cycles.

**Routine blood test, blood chemistry, coagulation function, myocardial function and urinalysis must be performed at screening and within 3 days prior to drug administration every treatment cycle. When the aforementioned laboratory tests and study drug administration are scheduled on the same day, the study drug administration must be scheduled only after the test results are obtained. Data from screening period should be completed on Day -7 ~ Day -1, and it is not necessary to perform the test again before the first administration (C1D1). Routine blood tests will be performed on Day 8 (±3 days) of each treatment cycle during treatment with carboplatin, and close attention should be paid to bone marrow suppression.

e. Bulgarian subjects must undergo tuberculosis testing for active and latent tuberculosis using a testing method as per local standard practice (as requested by the Bulgarian Drug Agency for Bulgarian subjects).

Central Laboratory Tests

PK and ADA samples of HLX10 or placebo are collected and sent to the central laboratory for evaluation. PK and ADA samples for HLX10 or placebo will be collected at the following time points:

Within 7 days pre-dose in Cycle 1, within 3 days pre-dose in Cycles 2, 4, 6, 8 and every 4 cycles thereafter, within 2 hours after the end of dosing in Cycles 1 and 8 of treatment period (for PK only), and at EOT visit and safety follow-up.

Table 5: Blood Sample Collection Time Points

Study visits		Blood sampling	Pharmacokinetics[a]	Anti-drug antibody[b]
Treatment period	Cycle 1	Within 7 days pre-dose	X	X
		Within 2 hours post-dose	X	-
	Cycle 2	Within 3 days pre-dose	X	X
	Cycle 4	Within 3 days pre-dose	X	X
	Cycle 6	Within 3 days pre-dose	X	X
	Cycle 8	Within 3 days pre-dose	X	X
		Within 2 hours post-dose	X	-
	Every 4 cycles thereafter	Within 3 days pre-dose	X	X
Discontinuation		-	X	X
Safety follow-up		-	X	X

a. Blood samples for HLX10 PK are collected within 2 hours after the end of HLX10 or placebo administration in Cycles 1 and 8 of the treatment period.
b. **ADA samples will only be collected pre-dose** and procedures are described in the laboratory manual.

Tumor imaging:

Imaging studies in this trial include CT or MRI. Images will be assessed by the IRRC according to RECIST 1.1 (see Appendix 2-1: Response Evaluation Criteria in Solid Tumors (RECIST 1.1)). The parameters (such as slice thickness and field of view) used for all follow-up imaging should be consistent with those at baseline. CT/MRI scans must meet the criteria for imaging lesions in the corresponding organ system.

Subjects should undergo CT or MRI (including brain, chest, abdomen, pelvic cavity and any other sites suspected of having tumor lesions) at screening (within 4 weeks pre-dose), every 6 weeks (± 7 days) during the first 48 weeks after the start of study treatment, and every 9 weeks (± 7 days) after week 48 (if baseline brain CT/MRI shows that brain metastasis is not present, the subject should have follow up brain imaging only if clinically indicated at the discretion of the investigator. If baseline brain CT/MRI has confirmed CNS metastasis, continuous brain imaging test should be carried out as part of the regular RECIST evaluation assessments).

At **screening**, bone scans are required for all subjects. Positive scans should be confirmed by CT/MRI, and re-examinations are determined by the investigator according to clinical needs during the treatment period. Brain MRI is also required at screening, but for subjects with contraindication, brain CTs are acceptable. The investigator assesses the tumor images according to RECIST 1.1 and iRECIST (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation. The IRRC assess the tumor images according to RECIST 1.1. If tumor assessment has been performed within 28 days prior to the first dose by the same methods and devices in the same hospital, it may serve as the baseline tumor assessment.

Tumor imaging studies are conducted every 6 weeks (± 7 days) for the first 48 weeks **after the start of study treatment** and every 9 weeks (± 7 days) after week 48, regardless of dose delay.

At the EOT visit, if tumor imaging has been performed within the last 4 weeks, a re-test is not required. Note: For all tumor imaging timepoints, investigator must assess all the tumor images according to RECIST 1.1 and iRECIST.

For subjects who discontinued for reasons other than disease progression, imaging assessments are to be continued as scheduled (at the same frequency as if the subject have remained on study treatment, i.e., every 6 weeks (± 7 days) for the first 48 weeks and every 9 weeks (± 7 days) after 48 weeks), until disease progression, initiation of new antineoplastic therapy, withdrawal of ICF, death, or end of study, whichever occurs first.

Biomarker sample collection:

At screening, blood samples and tumor tissue samples must be collected for biomarkers detecting. Patients must provide tumor tissues that meet the requirements for the determination of PD-L1 expression levels. The patients are recommended to provide formalin-fixed tumor tissue samples, paraffin-embedded tumor specimens (preferred), formalin-fixed paraffin-embedded (FFPE), tumor specimens or newly prepared unstained serial tissue sections (preferably adhesive slides) within 6 months prior to the first dose of study medication. A relevant pathology report must also be provided for the above specimens. Freshly collected specimens, radical resections, core needle biopsy, excisions, incisions, punch or clamp biopsies are acceptable (newly obtained tissues are preferred). Fine-needle aspirations (i.e., samples that lack a complete tissue structure and provide only cell suspension and/or cell smear), brush biopsies, and cell pellet samples from pleural or peritoneal effusions are unacceptable. For detailed requirements for tissue samples, see the laboratory manual.

8.2 Visit schedule

8.2.1 Screening Period (day -28 to day -1)

The ICF must be signed and dated by the subject or legal representative prior to conducting study-related procedures.

The screening period should not exceed 28 days, beginning from the subject signing and dating the ICF and ending when the subject is randomized or fails screening. In this study, one re-screening is allowed for ineligible subjects: in case of unqualified laboratory tests, one re-test can be performed within the screening time window, without giving a new screening number; for other conditions incompliant with the inclusion/exclusion criteria, subjects should be re-screened with a new screening number.

Subjects must complete the following study procedures or assessments at screening:

1) Signing ICF
2) Demographics and medical history
3) Prior and concomitant medications
4) Adverse events
5) Quality of life assessment (Day -7 to -1)
6) Echocardiography
7) 12-lead ECG
8) Complete physical examination
9) Height, weight and vital signs
10) ECOG scores (Day -7 to -1)
11) Local laboratory tests: routine blood test, serum biochemistry, coagulation, myocardial function, urinalysis, thyroid function, pregnancy test (for females of childbearing age only), virology and tuberculosis screening (as requested by the Bulgarian Drug Agency for Bulgarian subjects). Tests other than virology should be completed within 7 days before randomization
12) Tumor imaging:

    CT or MRI should be performed at screening (on sites including brain, chest, abdomen, pelvic cavity and any other sites suspected to have tumor lesions). At screening, bone scans are required for all subjects. Positive scans should be confirmed by CT/MRI. Brain MRI is also required at screening, but for subjects with contraindication, brain CTs are acceptable. If tumor assessment has been performed within 28 days prior to the first dose by the same methods and devices in the same hospital, it may serve as the baseline tumor assessment

13) Biomarker sample collection: Tumor tissue and blood samples are collected for biomarker

detection

Note: All reports from diagnostic procedures, which were performed before the ICF is signed and as part of the standard of care in the region and the examination methods/devices meet the study requirements might be used for the eligibility evaluation during the screening. This option restricted to those cases only, where the patient has given written confirmation that he/she consent to use his/her diagnostic reports of performed procedures before the date of ICF signature for eligibility evaluation of the actual study.

8.2.2 Treatment Period

Initial treatment visit

The initial treatment period begins with the subject's enrollment, and the first dose should be administered within 3 days after randomization. Study drugs are given every 3 weeks until disease progression, intolerable toxicity, discontinuation decided by the subject or the investigator, death, withdrawal of informed consent, pregnancy, noncompliance with protocol or procedure requirements, administrative reasons, or other reasons specified in the protocol, whichever occurs first. See Figure 1 "Schematic of study treatment" for details.

Subjects will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each subject. Also, subjects are assessed for toxicity prior to each dose; doses are only given when clinical assessments and local laboratory tests are acceptable.

The following study procedures must be completed at each visit during initial treatment period:

1) Concomitant medications
2) Adverse events
3) Quality of life assessment: prior to the first dose and every other subsequent dosing cycle (i.e., pre-dose in Cycles 1, 3, 5, 7, etc.) until EOT. Re-assessments are not required for subjects who had a quality of life assessment on Day -7 to Day -1 of the screening period
4) 12-lead ECG
5) Symptom-oriented physical examination
6) Weight and vital signs
7) ECOG scores
8) Survival status
9) Local laboratory tests: routine blood test, serum biochemistry, coagulation, myocardial function, urinalysis, thyroid function, pregnancy test (for females of childbearing age only)

and virology (if necessary)

- Routine blood test, biochemistry, coagulation, myocardial function and urinalysis should be performed within 3 days pre-dose in each treatment cycle; for combined chemotherapy, routine blood tests should be performed on Day 8 (± 3 days) of each treatment cycle.
- Thyroid function must be tested at the local site within 3 days pre-dose every 2 cycles.
- Serum pregnancy test must be performed for women of childbearing age at the local site within 3 days pre-dose every 2 cycles during the treatment period.
- In case of HBV DNA (-) and: 1) HBsAg (+), or 2) HBcAb (+) and HBsAg (-) at baseline, HBV antibody and HBV DNA should be tested every 2 cycles during the treatment period. In case of HCV antibody (+) and HCV RNA (-) at baseline, HCV antibody and HCV RNA should be tested every 2 cycles during the treatment period.

For aforementioned laboratory tests scheduled on the same day as study treatment, the study treatment can be arranged only after the test results are obtained

10) Central laboratory assessments: including HLX10 or placebo-PK, HLX10 or placebo-ADA sample collections
11) Study treatment
    Study drugs, including HLX10/placebo, carboplatin and etoposide, are administered on Day 1 of each cycle after all clinical and laboratory operations/assessments are completed.
12) Tumor imaging assessments
    CT or MRI should be performed every 6 weeks (± 7 days) during the first 48 weeks after the start of study treatment, and every 9 weeks (± 7 days) after week 48 on sites including brain, chest, abdomen, pelvic cavity and any other sites suspected to have tumor lesions (if the baseline brain CT/MRI shows that brain metastasis is not present, the subject should have follow-up brain imaging only if clinically indicated at the discretion of the investigator. If the baseline brain CT/MRI confirms CNS metastasis, a continuous brain imaging test should be carried out as part of the regular RECIST evaluation assessments); examination methods at the same site should be consistent as much as possible throughout the study; if there are no contraindications, contrast agent should be used. The investigator should assess the tumor images according to RECIST 1.1 and iRECIST (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation. The IRRC should assess the tumor images according to RECIST 1.1.

Post-PD treatment visit (Optional)

Initial treatment should be discontinued when they have evidence of disease progression as assessed by RECIST 1.1., if a subject has 1st disease progression, and is clinically stable, and

tends to receive 2nd line chemotherapy treatment subsequently (The selection of 2nd line chemotherapy may refer to the NCCN guidelines or the ESMO guidelines), he/she may continue the post-PD treatment assignment blinded at the discretion of the investigator and after appropriate discussion with the patient and obtaining the supplementary informed consent.

After comprehensive assessment by investigator, subjects would continue to receive benefit from their assigned treatment in addition to 2nd line chemotherapy may be eligible to continue to receive their assigned treatment in the post-PD treatment period (Optional) until the 2nd disease progression, intolerant toxicities, death, withdraw consent, or lost to follow-up. Subjects must not initiate treatment with HLX10 or placebo in post-PD treatment any earlier than 21 days and more than 12 weeks after their last dose of initial treatment (including chemotherapy) regardless of the time of progression.

The tumor image used to determine disease progression can be used as the new baseline image for the post-PD treatment period if 1) within 28 days prior to receiving the first dose of HLX10 or placebo therapy and 2) No study treatment between the image and first dose of HLX10 or placebo therapy, otherwise a new baseline image must be performed prior to HLX10 or placebo treatment. Subjects will be also monitored for safety and tolerability during the post-PD treatment period. All assessments must be performed and documented for each subject as the same as initial treatment period.

An objective response or progression of disease that occurs during the post-PD Treatment Period for a subject will not be counted as an event for the efficacy analysis of either endpoint in this trial.

The visits and following assessments are recommended for post-PD treatment period at each follow-up visit:

1) Concomitant medications
2) Adverse events
3) 12-lead ECG
4) Symptom-oriented physical examination
5) Weight and vital signs
6) Documenting subsequent anti-tumor therapies
7) ECOG scores
8) Survival status
9) Local laboratory tests: routine blood test, serum biochemistry, coagulation, myocardial function, urinalysis, thyroid function, pregnancy test (for females of childbearing age only) and virology (if necessary)

- Routine blood test, biochemistry, coagulation, myocardial function and urinalysis should be performed within 3 days pre-dose in each treatment cycle; for combined chemotherapy, routine blood tests should be performed on Day 8 (± 3 days) of each treatment cycle.
- Thyroid function must be tested at the local site within 3 days pre-dose every 2 cycles.
- Serum pregnancy test must be performed for women of childbearing age at the local site within 3 days pre-dose every 2 cycles during the treatment period.
- In case of HBV DNA (-) and: 1) HBsAg (+), or 2) HBcAb (+) and HBsAg (-) at baseline, HBV antibody and HBV DNA should be tested every 2 cycles during the treatment period. In case of HCV antibody (+) and HCV RNA (-) at baseline, HCV antibody and HCV RNA should be tested every 2 cycles during the treatment period.

For aforementioned laboratory tests scheduled on the same day as study treatment, the study treatment can be arranged only after the test results are obtained

10) Central laboratory assessments: including HLX10 or placebo-PK, HLX10 or placebo-ADA sample collections
11) Study treatment
    Investigational product (HLX10/placebo) are administered on Day 1 of each cycle after all clinical and laboratory operations/assessments are completed.
12) Tumor imaging assessments
    CT or MRI should be performed every 6 weeks (± 7 days) during the first 48 weeks after the start of study treatment, and every 9 weeks (± 7 days) after week 48 on sites including brain, chest, abdomen, pelvic cavity and any other sites suspected to have tumor lesions; (if the baseline brain CT/MRI shows that brain metastasis is not present, the subject should have follow-up brain imaging only if clinically indicated at the discretion of the investigator. If the baseline brain CT/MRI confirms CNS metastasis, a continuous brain imaging test should be carried out as part of the regular RECIST evaluation assessments); examination methods at the same site should be consistent as much as possible throughout the study; if there are no contraindications, contrast agent should be used. The investigator should assess the tumor images according to RECIST 1.1 and iRECIST (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation.

8.2.3 End-of-Treatment Visit

For any subject withdrawing from the study or terminating the study regardless of causality, an EOT visit should be performed, where possible, in 7 days after the end of the treatment is learned of or confirmed (and should be done prior to initiation of any new anti-tumor treatment in the subject). During the visit, the investigator shall collect the following information.

1) Concomitant therapy
2) Adverse events
3) Quality-of-life assessment: One quality-of-life assessment should be performed at this visit if such assessment has never been done in the past 3 weeks
4) 12-lead ECG
5) Symptom-oriented physical examination
6) Body weight and vital signs
7) ECOG score
8) Survival status
9) Local laboratory tests: including routine blood test, serum chemistry test, coagulation test, myocardial function, routine urine test, thyroid function test, pregnancy test (in women of child-bearing age only), and virological test (when necessary)

   Note:

   Thyroid function: If no more than 3 weeks have elapsed since the last thyroid function test, a repeat test is not required.

   HBV/HCV:

   - If at screening (baseline): HBV DNA (-), and 1. HBsAg (+), or 2. HBcAb (+), HBsAg (-), and it has been more than 3 weeks since the last test, then HBV DNA should be tested at treatment termination visit.
   - If at baseline: 1. HCV antibody (+), and HCV RNA (-), or 2. HCV RNA (+), and it has been more than 3 weeks since the last test, then HCV antibody and HCV RNA should be tested at treatment termination visit.
10) Central laboratory assessment: including HLX10 or placebo-PK blood sampling and HLX10 or placebo-ADA blood sampling
11) Radiologic tumor assessment: If any radiologic tumor assessment has been conducted during the first 4 weeks, then it may be unnecessary to repeat radiologic tumor assessment at the termination visit.

8.2.4 Follow-up Period

After the EOT visit, subjects will be followed up. If a subject terminates the study not because of PD, then radiologic assessment should be further performed according to an established schedule, where possible, until disease progression, initiation of a new anti-tumor therapy, ICF withdrawal, death or study completion (whichever occurs first).

Safety follow-up period

Subjects should be subjected to safety follow-up in 90 days after the last study drug administration, and AEs in subjects will be collected. Each subject shall come to the study center

for safety follow-up 30 (±7) days after the last study drug administration; if the EOT visit is delayed regardless of causality 30 (±7) days after the final study treatment, then the safety follow-up visit will no longer be performed. One safety follow-up should be performed by phone 90 (±7) days after discontinuation in each subject, in which information of the subject about AEs and AE-related concomitant therapy only will be collected. If the patient starts a new anti-tumor therapy during AE collection period, only AE information related to the study treatment need be collected after the initiation of the new anti-tumor therapy. Safety information should be acquired by phone with a window period of ±7 days. Safety follow-up assessment 30 (±7) days after discontinuation includes:

1) Concomitant therapy
2) Adverse events
3) Quality-of-life assessment
4) 12-lead ECG
5) Symptom-oriented physical examination
6) Body weight and vital signs
7) ECOG score
8) Documenting subsequent anti-tumor therapies
9) Documenting survival status
10) Local laboratory tests: including routine blood test, serum chemistry test, coagulation test, myocardial function, routine urine test, thyroid function test, pregnancy test (in females of child-bearing age only), and virological test (when necessary)

    Note:

    Thyroid function: If no more than 3 weeks have elapsed since the last thyroid function test, a repeat test is not required.

    HBV/HCV:

    - If at screening (baseline): HBV DNA (-), and 1. HBsAg (+), or 2. HBcAb (+), HBsAg (-), and it has been more than 3 weeks since the last test, then HBV DNA should be tested at safety follow-up.
    - If at baseline: 1. HCV antibody (+), and HCV RNA (-), or 2. HCV RNA (+), and it has been more than 3 weeks since the last test, then HCV antibody and HCV RNA should be tested at safety follow-up.
11) Central laboratory assessment: including HLX10 or placebo-PK blood sampling and HLX10 or placebo-ADA blood sampling.

Survival follow-up period

During the survival follow-up period, subjects should be followed up until ICF withdrawal, death, the patient is lost to follow-up, study termination by the sponsor, or study completion, whichever occurs first.

The following assessments shall be done at each follow-up visit:

1) Documenting survival status.

2) Documenting subsequent anti-tumor therapies.

8.3 Study Assessments

Efficacy assessment

Except overall survival, other efficacy endpoints are evaluated based on tumor response as per RECIST 1.1 and iRECIST. Tumor assessment will be performed by qualified personnel in each study center and IRRC. Therapeutic decision will be made based on tumor response assessment verified by the investigator. These results will be reported in eCRF.

Tumor assessment schedule is not influenced by treatment interruption or any other event leading to imbalance in disease assessment time between treatment groups.

Progression-free survival (PFS) is defined as a period from randomization initiation through the first objective PD or death (on account of any cause without PD). Progression-free survival will be always obtained based on scan/assessment date instead of visit date.

Progression-free survival 2 (PFS2) is defined as time from randomization to second/subsequent objective tumor progression on next-line treatment or death from any cause.

Overall survival (OS) is defined as a period from randomization through death regardless of causality.

Objective response rate (ORR) is defined as the percentage of subjects whose best overall responses are evaluated as complete response (CR) or partial response (PR).

Duration of response (DOR) is defined as a period from the first documentation of response (CR or PR) through the first documentation of PD or death (whichever occurs first). Response termination date should be consistent with the date of PD or death regardless of causality for evaluation of PFS endpoint as per RECIST 1.1.

8.4 Safety Assessment

Safety assessments variables include AEs (including SAEs), laboratory tests (routine blood test, blood chemistry test, coagulation test, routine urine test, myocardial enzymogram, BNP/NT-proBNP and thyroid function test), 12-lead ECG, vital signs, and physical examination.

8.4.1 Adverse Events

8.4.1.1 Definition of AE

Adverse event (AE) is defined as any adverse medical event occurring in a subject after receiving a drug in a clinical trial, not definitely having causality to treatment. Therefore, an AE can be any clinically significant manifestation (e.g., a clinically significant outlier in laboratory findings), symptom or disease, regardless of relevance to the study drug.

In the event of any outlier, it should be determined according to the following criteria whether the objective outlier should be reported as an AE or not:

- The finding is associated with a symptom, and (or)
- The finding necessitates drug/surgery intervention, and (or)
- The finding leads to dose adjustment (out-of-protocol-specification dose adjustment) or
- The finding constitutes an AE in the opinion of the investigator or the sponsor

If none of the above criteria is satisfied, then repeated outliers alone will not constitute an AE. It is unnecessary to report any incorrectly reported finding as an AE.

Any concomitant disease, which is manifested upon signing ICF and does not worsen in either severity or onset frequency during the study, is defined as a baseline medical condition, rather than an AE/SAE. However, if such concomitant disease in a subject is exacerbated, resulting in any complication or increased onset frequency, then such exacerbation or complication should be documented as an AE correspondingly. The investigator shall ensure that any documented event term is able to reflect the change of this condition (e.g., “exacerbation of ...”).

8.4.1.2 Disease Progression

Progression of any underlying disease, i.e., underlying tumor, should not be reported as an AE, and if its explicit manifestation is consistent with suspected progression of the underlying tumor defined in RECIST 1.1 and a subject is admitted just because of progression of the underlying tumor, then this PD should not be reported as an SAE. If it cannot be verified that a symptom is completely due to progression of underlying tumor, or a symptom does not conform to expected manifestation of PD in this study, then the progressing clinical symptom can be reported as an

AE. If it cannot be verified that an AE is caused by underlying tumor only, then this AE should be reported as an AE/SAE.

8.4.1.3 New tumor

Onset of any new tumor should be regarded as an SAE. New primary tumor refers to a cancer that is not a dominant cause of study drug treatment and is discovered after subject enrollment.

8.4.1.4 Death

All deaths occurring during the study or during follow-up period following the final dose of the study drug as specified in the study protocol have to be reported according to the following requirements:

- The cause of death (confirmed to be PD-induced or non-PD-induced) should be reported as an SAE and the death should be recorded as event outcome. The SAE report needs to be submitted to the clinical research associate (CRA)/clinical site manager (CSM), the sponsor, or a representative of the sponsor within 24 hrs.
- Any death from unknown cause should be reported as an SAE with the comment "death from unknown cause". The cause of death should be further explained during follow-up. An autopsy may help assess the cause of death. If an autopsy is performed, the autopsy report should be submitted to the sponsor's pharmacovigilance team or its representative as soon as possible.

8.4.1.5 Drug Overdose

Drug overdose means that a subject receives (intentionally or accidentally) a drug dose in excess of the dose specified in the protocol. In the event of drug overdose, appropriate symptomatic and supportive therapies may be performed in the subject. Any overdose-induced adverse reaction should be reported to CRA/CSM and included in a standard AE report.

Any overdose 3 times of the prescribed dose should be reported along with any AE and laboratory data

8.4.2 Serious Adverse Events

Serious adverse event: AEs occurring during a clinical trial in conformity with any or more of the following circumstances should be deemed as SAEs:

1) Leading to death

2) Life-threatening (AE occurrence leads to an immediate risk of subject death, not including those AEs that may lead to death after PD, e.g., drug-induced hepatitis without liver failure)
3) Necessitating hospitalization or prolonged length of stay; if a subject develops a discomfort or disease prior to study enrollment and is planned to be admitted for treatment and/or surgery before or during the study but does not present with exacerbation in an unexpected manner during the study, then this event will not be classified as an SAE
4) Leading to permanent or serious disability/insufficiency
5) Leading to congenital malformation/birth defect
6) Other significant medical events: Based on scientific medical judgment, it has to be decided whether reporting is to be expedited or not, and if the significant medical event might not immediately threaten the life, lead to death or hospitalization but some medical measures have to be taken to prevent any of the aforesaid circumstances from occurring, then this event will be normally deemed serious. For example, important treatment in A&E or domestic anaphylactic bronchospasm, non-nosocomial cachexia or convulsion, drug dependence or addiction, etc.

Note: Hospitalization or prolonged hospitalization on account of any non-AE cause/convenience (for purpose of health insurance reimbursement, etc.) or simply for clinical trial purpose does not meet the criteria for medical event and thus should not be considered as an SAE. However, each event leading to unexpected hospitalization or prolonged selective length of stay (e.g., any unexpected results of drug treatment) has to be documented and reported as an AE/SAE.

Hospitalization also includes nosocomial transfers to emergency/ intensive care unit (ICU) ward (such as transfer from pediatrics to internal medicine, transfer from internal medicine to ICU ward for patients with coronary heart disease, transfer from neurology to tuberculosis ward, etc.).

Hospitalization in the following institutions are excluded:

- Rehabilitation facilities
- Hospice care centers
- Short-term care facilities (e.g., care provided by nursing assistants)
- Specialized nursing facilities
- Nursing home
- Routine observation in A&E department
- Day surgery (outpatient treatment/diurnal surgery/diurnal operation)

Hospitalization or prolonged hospitalization due to any of the following causes is not classified as an SAE:

- Hospitalization for treatment of any original disease unrelated to any new AE or

worsening of any original adverse disease (for example, inspection of persistent laboratory outliers existing prior to treatment);

- Hospitalization due to any non-medical cause (e.g., homelessness);
- Transactional hospitalization (e.g., routine checkup);
- Hospitalization specified in the study protocol (e.g., operation required for implementation of the study protocol);
- Voluntary hospitalization that will not give rise to any clinical AE (e.g., for elective plastic surgery);
- Treatment or surgery planned in the study protocol and (or) for individual subjects should be documented in baseline documents;
- Hospitalization specifically for use of the study drug.

Diagnostic and therapeutic non-invasive/invasive procedures, such as surgeries, should not be reported as AEs. Nonetheless, if diseases that such operations are intended to treat meet the definition of AE, diseases should be reported as AEs. For example, acute appendicitis occurring during AE reporting should be reported as an AE, and appendectomy for treating the disease should be documented as treatment for this AE.

8.4.2.1 Drug-induced liver injury (DILI)

All cases confirmed on repeat testing as meeting the criteria, as described below, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. The event meeting the below criteria should be reported as serious adverse event.

Table 6: The abnormal liver function test (LFT) needed to be reported as an SAE

Baseline	AST or ALT and total bilirubin baseline values within the normal range	ALT or AST or total bilirubin values above the upper limit of normal
Treatment time	✧ ALT or AST≥ 3×ULN (upper limit of normal) ✧ Concurrent with a total bilirubin≥ 2×ULN ✧ And alkaline phosphatase≤ 2×ULN or not available ✧ And no evidence of hemolysis	✧ AST or ALT≥ 2 times the baseline values，and ≥ 3× ULN；or AST or ALT≥ 8× ULN (whichever is smaller) ✧ Concurrent with a total bilirubin≥ 2×ULN and increased by one upper limit of normal over baseline or > 3×ULN (whichever is smaller) ✧ And alkaline phosphatase≤ 2×ULN or not available ✧ And no evidence of hemolysis

8.4.3 Documentation of AEs

All AEs occurring in a period from signing ICF (either main or supplementary) through 90 days after the final administration of the study drug should be documented in corresponding AE pages in EDC. If a subject starts a new antineoplastic therapy during the AE collection period, only information on AEs related to study treatment are documented after the new antineoplastic therapy. The investigator shall provide all detailed information required to be completed, including date of onset, severity, action, outcome, and causality to the study drug. When collecting AE data, one has better recording diagnosis information (if possible), rather than recording a number of signs and symptoms. However, if a diagnosis is known but the patient still has other symptoms or signs not contributing to such diagnosis, then each symptom or sign should be documented separately.

All AEs/SAEs occurring in a period from signing ICF through 90 days after the final dose of the study drug (including chemotherapy drugs) or the start of a new anti-tumor treatment (whichever occurs first) should be documented, and the following information has to be collected:

- AE
- Onset date and end date of the AE
- CTCAE grade
- SAE or not
- Causality between the AE and the study drug as assessed by the investigator
- Actions taken with the study drug
- Therapeutic actions against the AE
- Outcome
- AESI or not

In addition, the following information will be collected for each SAE:

- Date when the AE meets SAE criteria
- Date when the investigator learns of the SAE
- Justification of SAE
- Date of discharge (if applicable)
- Potential cause of death (if applicable)
- Date of death (if applicable)
- Autopsy findings (if applicable)
- Assessment of causality between the AE and study operation
- Assessment of causality between the AE and other drugs
- Description of the AE

Note: If the investigator learns, after a subject has completed safety follow-up or withdrawn from the study, that the subject experienced any SAE (including death) and reasonably considers that this event is possibly related to the study drug, then the investigator should report it to the sponsor's pharmacovigilance team or representative.

8.4.3.1 Severity of AEs

National Cancer Institute's CTCAE V5.0 is used to document severity of AEs, classified in grades 1–5.

Table 7: CTCAE Description

Grade	CTCAE Description
1	Mild: No or mild symptom; only clinical or diagnostic observation is required; action is not needed.
2	Moderate: Small-scope, local or non-invasive action is needed; instrumental Activities of Daily Living (ADL) are restricted to appropriate ages*.
3	Serious or medically significant but not immediately life-threatening; necessitating hospitalization or prolonged hospitalization; incapacity; self-care ADL are restricted**.
4	Fatal result: Urgent action is to be taken.
5	AE-related death

ADL= Activities of Daily Living; AE=Adverse Event; CTCAE = Common Terminology Criteria for Adverse Events

*: Instrumental ADL are activities such as cooking, grocery shopping, making/receiving phone calls, and financial management.

**: Self-care ADL are activities such as bathing, dressing and undressing, feeding yourself, going to the restroom, taking pills, and leaving the bed.

Attention must be paid to distinguish severity from intensity of an AE. "Severe" is used to describe intensity, so a severe AE is not definitely an SAE. For example, headache may appear severe in intensity but cannot be classified as an SAE, unless it meets the criteria for SAE.

8.4.3.2 Causality between the AE and the study drug

The investigator will evaluate whether causality between the study drug and the AE is "related", "possibly related", "unlikely related", "unrelated", or "unknown". AEs other than "unlikely related" and "unrelated" are recorded as adverse reactions.

- related:
  - Reasonable time relation+
  - In conformity with a known type of adverse reactions+
  - AE is absent or attenuated after interruption or dose reduction+
  - AE reoccurs after repeated medication+
  - Other reasonable interpretations –

- Possibly related:
  - Reasonable time relation+
  - In conformity with a known type of adverse reactions±?
  - AE is absent or attenuated after interruption or dose reduction±?
  - AE reoccurs after repeated medication±?
  - There is a probability of any other cause leading to this AE±?
- Unlikely related:
  - Reasonable time relation-
  - In conformity with a known type of adverse reactions-
  - AE is absent or attenuated after interruption or dose reduction±?
  - AE reoccurs after repeated medication±?
  - There is a probability of any other cause leading to this AE±?
- unrelated:
  - Reasonable time relation-
  - In conformity with a known type of adverse reactions-
  - AE is absent or attenuated after interruption or dose reduction-
  - AE reoccurs after repeated medication-
  - There is a probability of any other cause leading to this AE+
- Unknown: Essential data for evaluation is unavailable

Table 8: Evaluation of Causality Between AE and Study Drug

	related	**Possibly related**	**Unlikely related**	**unrelated**	**Unknown**
Reasonable time relation with the study drug	+	+	-	—	Essential data for evaluation is unavailable
Known type of drug reactions	+	±?	—	—	
Reaction is attenuated or absent after discontinuation	+	±?	±?	—	
Positive Rechallenge	+	?	?	—	
There is a probability of any other cause leading to this AE	-	±?	±?	+	
Note: + Yes – No ± Likely ? Unknown					

8.4.3.3 Determination of Expectedness

An unexpected AE refers to an event not in conformity with corresponding reference safety information of the drug in nature or severity. For investigational medicinal products, the predictability of an AE will be assessed based on whether the event is listed in the Investigator's Brochure. For comparators that are already approved for marketing, the predictability of an AE will be assessed based on whether the event is listed in the drug instructions.

8.4.4 Reporting of SAEs

All SAEs occurring during the clinical study should be reported immediately (or in 24 h after being informed) by the investigator to the sponsor or a representative designated by the sponsor. This time frame applies to additional information (follow-up information) of previously released SAE report, and initial report and follow-up report of pregnant cases, too. The sponsor's representative and the investigator share the responsibility of ensuring that all essential information is submitted within the above time frame.

For all SAEs, the investigator is obliged to acquire relevant information and submit it to the sponsor within the above-mentioned time frame of reporting. In addition, the sponsor may request the investigator to acquire more follow-up information quickly. Such information may be more detailed than the information shown in the AE report. In general, such information shall

include sufficiently detailed description of AEs so as to facilitate comprehensive medical assessment of the cases and independent assessment of causality. Moreover, the investigator must provide information about other potential causes of AEs, such as concomitant medications and complications.

In the event of subject death, a summary of autopsy findings (if any autopsy finding is available) has to be submitted to the sponsor or the representative designated by the sponsor as soon as possible.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

The investigator or any person-in-charge required by local authority shall abide by local regulatory regulations on SAE reporting and report SAEs to regulatory bodies, Institutional Review Board (IRB) or Independent Ethics Committee (IEC), as per request.

8.4.5 Follow-up of AEs

All AEs and SAEs that occur in each subject throughout the study should be actively followed up. Even if such events persist after discontinuation or study termination, the investigator should follow them up until all events meet any of the following criteria:

1) The event is recovered (or returns to the baseline level);
2) The event is stable (as predicted by the investigator, the AE will not be further improved or exacerbated);
3) Failing to acquire more information (the subject refuses to provide more information, or it is evidenced that the subject is lost to follow-up even after the maximum effort has been made).

The sponsor reserves a right to request (if necessary) more information of current AE/SAEs from any subject at the end of the study.

8.4.6 Adverse event of special interest (AESI)

AESIs are events of scientific and medical concern related to use of the investigational product that may need to be closely monitored and communicated to sponsors by investigators. AESI can be a serious or non-serious event. The AESI expedited report enables continuous monitoring of these events in order to describe and understand their association with the drug used in the study.

In this study, AESI include infusion reaction (infusion-related adverse reactions, IRR) and immune-related adverse events (irAE).

Immune-related adverse event (irAE) refers to an AE that is related to drug exposure and in conformity with immune-mediated mechanism of action without any other definitive pathological factor. Serological, immunological and histological (biopsy) data should be used to support diagnosis of irAE when appropriate. Appropriate methods should be used to exclude pathological factors of irAE such as tumor, infection, metabolism, toxin, etc.
More detailed guidance on its assessment and treatment please refer to Appendix 8:NCCN Guidelines®: Management of Immunotherapy-Related Toxicities (2019 V2).

For any suspected irAE, related system functions need to be closely observed and adequate assessment shall be carried out to identify etiology and exclude other potential causes. In general, depending on severity of an AE, HLX10 (or placebo) should be suspended or permanently terminated, and/or symptomatic treatment (e.g., glucocorticoids) may be given. If the AE is not improved or is worsened after glucocorticoid therapy, one can consider increasing the dose of glucocorticoid and/or using any other systemic immunosuppressant. When grade of an AE is <1, dose of glucocorticoid can be reduced gradually, and the treatment has to persist for at least 1 month. When an AE is recovered to < grade 1 and dose of glucocorticoid is reduced to prednisone (or another drug with equal potency) with a daily dose <10 mg, HLX10 or placebo transfusion may continue. In the event of recurrence of any grade 3 or above irAE (except for endocrine system disorders), permanent discontinuation and study withdrawal have to be done immediately.

If an irAE meets the SAE criteria, it should be handled in accordance with the relevant procedures of SAE reporting. For the following AEs, they should be reported to the sponsor within 24 hrs (adverse event of special interest) even if they do not meet the SAE criteria (with no need to report to the relevant regulatory and Ethics Committee):

≥ Grade 3 of infusion-related reaction

≥Grade 2 of colitis, uveitis, interstitial pneumonia, myocarditis

≥3 Other immune-related adverse events.

8.4.7 Pregnancy

Each fertile subject shall take appropriate contraceptive measures in a period from signing ICF through at least 6 months after the final dose of the study drug.

Once becoming pregnant during the study, female subjects shall immediately discontinue the study drug and notify the investigator. The investigator shall report any pregnancy event to the sponsor (or an authorized representative) in 24 hours after becoming aware of the pregnancy. Monitoring of the subject will persist until the end of pregnancy. Any pregnancy that occurs within 6 months after the final dose of the study drug should be reported to the investigator.

If any female subject or the spouse of any male subject gets pregnant during the treatment and within 6 months after the final dose of the study drug (whichever occurs first), the investigator should complete a Pregnancy Report in 24 h after becoming aware of the pregnancy, report to the sponsor (or an authorized representative), and record in eCRF to facilitate outcome follow-up. Any pregnancy event should be followed up until 30 days after the end of pregnancy.

Any AE/SAE occurring in a mother or newborn during pregnancy, such as natural abortion or termination of pregnancy for medical reasons, birth defects or congenital malformation of newborns, malformation and anomalies of death fetuses, complications of mothers and newborns, etc., should be documented and reported according to "Documentation of AEs" and "Reporting of SAEs".

9 Statistical Considerations

9.1 Statistical Hypotheses

See statistical analysis plan for further details.

9.2 Sample Size Determination

The randomization ratio for this study is 2:1. The sample size is estimated based on the assumption that the median OS for treatment with placebo + chemotherapy (Carboplatin–Etoposide) is 10 months and the hazard ratio (HR) of (HLX10 + chemotherapy) group versus the control group is 0.7, and it is further assumed that when the enrollment period is 24 months and the whole study period is 34 months, to achieve a confidence level of 85% at an overall significance level $\alpha = 0.05$ (two-sided), at least 342 OS events have to be observed. Considering a dropout rate of 20%, a total of 567 subjects (378 in treatment arm and 189 in control arm) need to be enrolled in the 2 arms.

It is planned in this study that, when the 378 subjects (about 2/3 of the number of subjects planned to be enrolled) was enrolled under supervision of the Independent Data Monitoring Committee (IDMC), the sponsor will consider performing a blinded sample size estimation, and if the blinded overall median OS is lower than the expected value, then the sponsor will communicate with principal investigator and regulatory authorities about the necessary increase in the sample size (number of OS events).

9.3 Populations for Analyses

For purposes of analysis, the following analysis sets are defined:

Population	Description
Enrolled	All participants who signed the ICF (including screening failures).
Intent-to-treat (ITT) set	The ITT comprises all participants to whom study intervention has been randomized. Statistical analyses will be based on study intervention groups as per randomization, irrespective of the study intervention actually received. The ITT population will serve as the primary population of efficacy assessment in this study. ITT population will be analyzed based on treatment arms.
Per Protocol Analysis Set (PPS)	The PPS comprises a subset of the ITT. The PPS consists of all randomized subjects undergoing at least one post-treatment tumor assessment without any major protocol deviation that impacts the primary efficacy significantly. The PPS will be used to demonstrate robustness of results for the efficacy endpoint.
Safety Set	The Safety Set consists of all participants who received at least one dose of study intervention. Participants will be analyzed according to the study intervention they actually received. The safety set is the primary population for safety endpoint analysis. A precise definition of “as actually received” will be added in the Statistical Analysis Plan (SAP).
PK Analysis Set (PKS)	The PKS consists of all participants who received at least one dose of study intervention with at least one post-dose concentration measurement at scheduled PK time points without any major protocol violation that may impact the PK assessment significantly. The PK analysis set will be used for PK analysis.

9.4 Statistical Analyses

All statistical analyses will be performed using SAS version 9.2 (or later) statistical analysis software. For continuous variables, standard descriptive statistics include median, mean, standard deviation, minimum, and maximum, while categorical variables include the quantity and percentage.

Demographic information, baseline profile data, medical history, and concomitant medications of all randomized subjects will be summarized using descriptive statistics depending on the randomization approach.

The medication compliance data of the investigational product (HLX10 or placebo combined with Carboplatin–Etoposide) will be summarized using descriptive statistics in groups.

The detailed statistical analysis plan and methodology shall be elaborated in the Statistical Analysis Plan (SAP).

Demographic information, baseline profile data, medical history, and concomitant medications of all randomized subjects will be summarized using descriptive statistics depending on the randomization approach.

The medication compliance data of the investigational product (HLX10 or placebo combined with Carboplatin–Etoposide) will be summarized using descriptive statistics in groups.

Below is a summary of planned statistical analyses of the primary and secondary endpoints. Further details are presented in the SAP.

9.4.1 Efficacy Analyses

Analyses of the primary efficacy endpoint and the secondary efficacy endpoints will be performed for both the ITT and PPS, mainly on the ITT.

9.4.1.1 Analysis of primary efficacy endpoint

Overall survival (OS): Defined as a period from randomization through death regardless of causality. Data of patients without a death record will be censored on the last known survival date. The between-group comparison of OS is performed by a stratified log-rank test with the following stratification factors: PD-L1 expression level (negative: TPS <1%, positive: TPS ≥1%, or not evaluable/not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years); a stratified COX proportional risk model will be used to estimate HR and its 95%

confidence interval (CI); the Kaplan-Meier method will be used to estimate the median, and the Kaplan–Meier curve will be plotted.

9.4.1.2 Analysis of secondary efficacy endpoints

Progression free survival (assessed by the IRRC as per RECIST 1.1): PFS is defined as a period from randomization initiation to the first documentation of PD or death regardless of causality (whichever occurs first). Censor rules will be defined in SAP. The PFS will be analyzed using the same method as that for primary endpoints.

Progression-free survival assessed by the investigator as per RECIST 1.1 and iRECIST. Its statistical method is the same as that for primary efficacy endpoints.

Progression-free survival 2 (assessed by the investigator based on RECIST 1.1). PFS2 is defined as time from randomization to second/subsequent objective tumor progression on next-line treatment or death from any cause. It will be analyzed using the same method as that for PFS.

Objective response rate (ORR) assessed by the IRRC and the investigator as per RECIST 1.1 separately: Defined as the percentage of subjects whose best overall responses are evaluated as CR or PR. The stratified Cochran-Mantel-Haenszel method is used to test the between-group variation in the ORR and to estimate the odds ratio and its 95% CI.

Duration of response (DOR): Defined as a period from the first documentation of response (CR or PR) through the first documentation of PD or death (whichever occurs first). The DOR will be analyzed only for patients whose best overall responses are evaluated as CR or PR. Data of patients not experiencing PD or death after achieving response will be censored on the day of the final tumor assessment; if no tumor assessment is performed after response achievement, then data of such patients will be censored on the day of tumor assessment when response is achieved. The Kaplan-Meier method is used to estimate the median and plot the Kaplan-Meier curve.

9.4.1.3 Subgroup Analyses

To assess the consistency of the study PFS and OS, results in subgroups will be examined. The following subgroups will be considered:

- Demographics (e.g., age, sex, and region/race/ethnicity, etc.)
- Baseline prognostic characteristics (e.g., ECOG performance status, smoking status, presence of brain metastases, etc.)

To explore the efficacy under different PD-L1 expression level, the following subgroups will be examined.

- PD-L1 expression level based on tumor proportion scores (positive TPS ≥1% vs. negative TPS <1%)
- PD-L1 expression level based on combined positive score (positive CPS ≥1% vs. negative CPS < 1%)

Summaries of PFS and OS, including unstratified HRs estimated from Cox proportional hazards models will be displayed in a forest plot. Kaplan-Meier estimates of median PFS and OS will be produced separately for each level of the categorical variables for the comparisons between treatment arms.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Set.

AEs will be described according to Medical Dictionary for Regulatory Activities (MedDRA) terms and graded according to CTCAE v5.0. Adverse events occurring during or after the first dose of study drug will be summarized by CTCAE grade. Treatment-emergent adverse events (TEAEs) and concomitant medications in the trial will be summarized separately by treatment arm. The clinical laboratory parameters, ECOG PS scores, vital signs, physical examination, and ECG will be summarized by the treatment group and study visit. Values observed and changes from baseline will be descriptively reported by visit in this trial.

9.4.3 Pharmacokinetic Analyses

The statistical method will be detailed in the SAP.

9.4.4 Immunogenicity Analyses

The statistical method will be detailed in the SAP.

9.4.5 Biomarker Analyses

During the screening for this study, tumor tissues of subjects will be collected for assay of the PD-L1 expression level, MSI and TMB; blood samples of subjects will be collected for assay of the MSI and TMB. The primary objective is to assess the relations among the PD-L1 expression and MSI, TMB and efficacy.

9.4.6 Analysis of Subject-reported Outcome Variables

The health status and self-perceived health of each patient will be documented in the form of EQ-5D-5L scale, EORTC QLQ-C30 scale, and EORTC QLQ-LC13 scale.

Descriptive statistics are based on the allocation for the scale scores, subscale scores, and individual scores at each visit and their changes from baseline. The analytical methods will be detailed in the SAP. Unless otherwise specified, PRO analysis of all data will be performed based on the ITT set.

9.5 Interim Analyses

An IDMC will be established for this study for interim analysis. This study plans to carry out an interim analysis. The O'Brien-Fleming type alpha-spending function (using the Lan-DeMets method to approximate) shall be used to control overall type I error rate. The stopping boundary for OS interim and final analyses are shown in Table 9.

- The first interim analysis is scheduled to be conducted when 66% (approximately 226) of OS events are observed, and the interim analysis will assess the safety and efficacy of the trial group. The α for the first interim analysis will be 0.012 (two-tailed) based on the O'Brien-Fleming type alpha-spending function.
- The final analysis of OS will be performed when a target number of OS events (approximately 342) are observed, and the α for the final analysis will be 0.046 (two-tailed) based on the O'Brien-Fleming type alpha-spending function.

Table 9 Analysis Timing and Stopping Boundary of Overall Survival

Analysis Timing	Information Fraction (Number of Events)	Estimated Time (month)	Stopping Boundary (p-value)
OS interim analysis	66% (226)	19	<0.012
OS final analysis	100% (342)	34	<0.046

The SAP will describe the planned interim analyses in greater detail.

9.5.1 Independent Data Monitoring Committee (IDMC)

The IDMC will be established to independently oversee the blinded sample size re-estimation procedure; to review safety data at regular intervals in order to safeguard the interests of study

participants; and to monitor the overall conduct of the study. Responsibilities of the IDMC will be fully documented in the IDMC Charter.

10 Supporting Documentation and Operational Considerations

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Data Management

Establishment of Database

Data from this clinical trial will be collected through remote data entry in the eCRF. The data administrator shall design a database and test it with simulation data or real eCRF data to ensure that the database is accurate and correct.

Data Checks

During data management, data checks include the edit check, manual check, medical check, and statistical pre-analysis check. All the data query will be displayed in the EDC system in the form of electronic query for the study site to answer. The query will be closed if the answer is acceptable. If any data query is not resolved or a new query arises after the database is updated based on the answer to the previous data query, then the investigator or clinical research coordinator shall answer again. The above process will be repeated until all data in the database is checked to be correct.

Database Lock

The data administrator shall draft a data review report pursuant to the trial protocol, data review criteria, and the database. The project manager shall convene a data review meeting attended by the sponsor, principal investigator, statistician, and data administrator to review the data, and a data review resolution shall be jointly signed by the representatives of the participants. The data administrator shall implement data locking upon approval by all the participants. The locked data will be submitted to the statistician for statistical analysis.

The data can be locked when the following conditions are satisfied.

1) All data has been collected and entered into the database
2) All codes have been checked and verified
3) All data queries have been resolved (including queries proposed in data review)
4) Data review has been completed
5) Source data verification has been completed
6) Verification of SAEs has been completed

7) Signatures of all investigators have been obtained
8) Analyzable cases have been defined and stored in the final analysis database
9) The SAP has been signed

10.1.2 Regulatory and Ethical Considerations

This trial shall be implemented in accordance with the good clinical practice (GCP), Declaration of Helsinki, relevant regulations, and review comments of the Institutional Review Board.

The investigator shall ensure that this trial is reviewed and approved by a qualified institutional review board in compliance with GCP. Prior to the trial, the investigator shall submit the trial protocol, informed consent forms, and other essential documents to the IRB for review and approval. The sponsor shall provide the study drug after receiving the approval from the IRB. Meanwhile, the IRB shall be informed of subsequent protocol amendments and SAEs occurring during the study that may impact the safety of subjects in the trial and preclude the subjects from study continuation. The investigator is obligated to report the trial progress to the IRB. In addition, the investigator must timely submit copies of all correspondences with the IRB to the sponsor. When reviewing and approving the trial protocol, the IRB must verify the protocol title and number, indicate and date the reviewed protocol documents. In the event of any additional amendment to the trial protocol and the ICFs during the trial, an additional written approval shall be obtained from relevant authorities according to relevant regulations.

10.1.3 Financial Disclosure

Investigators and sub-Investigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4 Informed Consent Process

Information related to this trial must be informed by the investigator both verbally and in writing. The subject has the right to know detailed information about the trial.

The ICF (together with the trial protocol) must be reviewed and approved by the Ethics Committee. If needed, the investigator shall be responsible for explaining the content of the ICF to the subject in a manner and wording that is understood by the subject. The subject should have sufficient time to read the informed consent before signing the informed consent officially.

The text in the final ICF should include the following content: The objectives of trial, the course and duration of the trial, the examination procedures, the expected benefits and risks of the subjects, and the subjects shall be informed that they may be assigned to the different groups in the trial; in the event of trial-related damages, the subjects may receive treatment and corresponding compensation; confidentiality principle of subject personal data, etc.

The ICF must be signed and dated by the subject, and the investigator who executed the informed consent process must also sign and date the ICF. One copy each of the ICF should be kept by the investigator and the subject. If important new information related to the study drug is found, a written amendment to the ICF must be submitted to the Ethics Committee for approval before obtaining consent from the subjects again.

10.1.5 Data Protection

The investigator is obligated to keep the subject anonymous. In the CRF or other documents, the subjects can be only identified with capitalized letters, numbers and/or codes, instead of names. The investigator must properly keep the Subject Enrollment Log documenting the codes, names, and residential addresses of the subjects. The investigator must keep strictly confidential any document that may reveal the identity of the subject.

10.1.6 GCP training

According to the GCP guideline, the CRA shall have the qualification accepted by the sponsor; before the clinical trial, the person in charge of the study site shall train the investigator on the trial protocol, so as to enable the investigator to become fairly familiar with this clinical trial protocol, master the GCP guideline, unify the documentation approach and evaluation criteria, and perform the trial in strict accordance with the protocol.

10.1.7 Data Quality Assurance

Prior to the formal initiation of the trial, the sponsor (or Contract research organization authorized by the sponsor) and the investigator shall discuss and develop a clinical study plan to guarantee the trial quality. The study personnel involved in this trial shall be trained on GCP.

Study drugs must be managed in each study site as per relevant standard operating procedures (SOP)s, which involve the receipt, retention, distribution, and recovery of the drugs.

In accordance with the GCP guideline, necessary steps must be taken during the design and implementation of this study to ensure the accuracy, consistency, integrity, and credibility of the collected data. All observations and outliers in the clinical trial shall be promptly and carefully

verified and recorded to ensure data reliability. Ensure that various instruments, devices, reagents, and reference standards in this clinical trial are in strict compliance with corresponding quality specifications and operate in the normal state.

The investigator will enter information required by the protocol into the CRF, and the monitor shall check if it is completely and accurately filled out and instruct the personnel in the study site to make amendments and supplements if necessary.

The drug regulatory authorities and the sponsor may authorize auditors to conduct systematic examination of activities and documents in connection with the clinical trial, so as to evaluate if the trial is carried out in accordance with the trial protocol, SOPs and relevant regulatory requirements, and if the trial data is documented in a timely, authentic, accurate, and complete manner. The audit shall be performed by personnel not directly involved in this clinical trial.

10.1.8 Audit

During the study, the sponsor may conduct a quality assurance audit for the study site, the study database, and the study documentation. The audit includes drug supply, required trial documents, documentation of the informed consent process, and consistency between the CRF and source documents, and so on. The content and scope of the audit can be added when needed. After being reasonably notified, the investigator shall accept the study-related audit by the auditors authorized by the sponsor, as well as the inspection by regulatory authorities.

In addition, the regulatory authorities may inspect the study as well.

10.1.9 Data Management/Coding

The departments of data management and biostatistics will process data generated in this clinical study according to relevant SOPs.

Data acquisition is performed by the personnel from a study site designated and authorized by the investigator. Before the study is initiated and any data of any subject in the study is entered into the EDC system, the investigator and all the personnel from the authorized study site must be trained properly, and appropriate safety measures shall be taken.

The monitor will compare the eCRF with source documents to ensure that there is no deviation between crucial data. All items, corrections, and changes have to be completed by the investigator or the personnel designated by the investigator. Relevant personnel of the study will raise queries and send to the investigator. In this regard, the EDC will be audited and tracked, which means the names of the study personnel, time, and date will be documented.

The investigator is responsible for maintaining source documents. These documents shall be checked by the monitor of the study during each monitoring visit. The investigator must submit one copy of complete eCRF including data of every subject receiving study medication, regardless of the treatment duration of the subject. The study and subject numbers shall be used to indicate explicitly all supporting documents submitted along with the eCRF, e.g., laboratory or hospital records. Any personal information including subject names shall be deleted or made illegible so as to keep the subject information confidential.

10.1.10 Documentation and Retention of Study Data

The investigator is obligated to maintain essential documents of the study (the protocol and protocol amendment, completed eCRFs, signed informed consent forms, important correspondence files, and all other supportive documents). The study site shall establish a plan to retain these documents for 5 years after study completion. The study site shall always retain these documents until at least 2 years after the investigational product is finally approved for marketing, and until at least 5 years after there is no pending approval or marketing authorization application for the investigational product, or after clinical development of this investigational product is formally terminated. These documents shall be retained for a longer time upon the request of any corresponding regulatory authority, or any hospital, institution, or private clinic involved in this study. Subject codes (subject names and corresponding study numbers) should also be retained for the same time period. As agreed by the sponsor, these documents can be transferred to another responsible party who must observe the document retention policy. The sponsor must be notified in writing of any transfer of documents. The investigator must contact the sponsor before disposing of any study record.

10.1.11 Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.12 Premature Termination of Study and Site Closure

The study may be terminated prematurely due to the following reasons. Written permissions of both the principal investigator and the sponsor are required for the early termination of the study, and results of the study shall be reported in accordance with the requirements of the protocol.

1. The study is unlikely to be completed within an acceptable time frame due to difficulties in subject enrollment;
2. The investigator questions the safety of the drug during the study and concludes that further study would pose serious risks to the subjects;
3. The principal investigator and the sponsor believe that the number and severity of AEs suggest a premature termination;
4. The efficacy fails to meet expectations and it is not necessary to continue the clinical trial;
5. The study is revoked by regulatory authorities;
6. The sponsor has the right to terminate the study at a certain study site in the event of:

- serious violations of GCP by the study site;
- repeated serious protocol violations by the study site;

Upon the termination of the study, all related records shall be kept for future reference.

10.1.13 Confidentiality and Publication Policy

All information about the trial (including but not limited to the following documents: the protocol, and the Investigator's Brochure) is the intellectual property of the sponsor and may not be disclosed to any third party not related to the trial. The investigator must recognize that the scientific or medical information obtained from this trial may be of commercial value to the sponsor. The investigator shall keep the information and data related to this trial confidential. If the investigator intends to publish the information related to this trial or the conclusions drawn from the trial, the investigator shall negotiate with the sponsor in advance and obtain the written consent of the sponsor. In order to protect its rights, the sponsor may request the investigator not to publish information related to the trial before the trial product is approved for marketing.

The sponsor has the right to publish or release information or data related to the trial or to report it to the drug administrative departments. If the sponsor needs to display the name of the investigator in the content published, released, or advertised, the sponsor shall obtain the consent of the investigator.

10.1.14 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). In the US: Following approval, the protocol amendment(s) will be submitted to the Investigational New Drug (IND) under which the study is being conducted.

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

10.1.15 Liability and Insurance

10.1.15.1 Responsibilities of the Investigator

The investigator's responsibilities mainly include but are not limited to:

1) Designing and signing a trial protocol with the sponsor through discussion, and reporting the protocol to the IRB for approval before implementation.
2) Scrutinizing, understanding, and strictly implementing the protocol.
3) Being knowledgeable about and familiar with the nature, function, efficacy, and safety of the investigational product (including information about the preclinical study for the product), as well as all new information related to the product discovered during the clinical trial.
4) Conducting the clinical trial in medical institutions equipped with adequate medical facilities, laboratory equipment, and staffing, as well as all facilities needed to handle emergencies to ensure the safety of the subjects. Ensuring the laboratory results are accurate and reliable.
5) Obtaining the consent of the medical institution or the competent authority, and ensuring that sufficient time is left to complete the clinical trial within the time limit set by the protocol. Explaining the data, regulations, and responsibilities concerning the trial to all staff participating in the clinical trial to ensure that a sufficient number of subjects meeting the requirements of the protocol are enrolled in the clinical trial.
6) Explaining to the subjects the details of the trial approved by the IRB and obtaining the ICF from the subjects.
7) Making medical decisions related to the clinical trial to ensure that the subjects receive appropriate treatment in case of AEs during the trial.
8) Taking necessary measures to ensure the safety of the subjects and putting on record such measures. Taking immediate and appropriate treatment measures for the subjects in case of any SAEs during the clinical trial, reporting the serious adverse event to the drug regulatory authorities, health administrative departments, the sponsor and the IRB, and making sure to

sign and date the report before submission.

9) Ensuring that data is recorded in the case history and the CRF in a true, accurate, complete, timely, and legitimate manner.
10) Accepting the monitoring and audit by the monitors and auditors dispatched by the sponsor, as well as the audit and inspection by the drug regulatory authorities to ensure the quality of the clinical trial.
11) Discussing with the sponsor the cost of the clinical trial and including it in the contract. Refraining from charging the subjects for the cost of the investigational product during the clinical trial.
12) Writing, signing, and dating a final report after the clinical trial is complete, and sending it to the sponsor.

10.1.15.2 Responsibilities of the Sponsor

The sponsor's responsibilities mainly include but are not limited to:

1) Obtaining approval from the China Food and Drug Administration (CFDA).
2) Initiating and applying for a clinical trial, as well as funding the trial.
3) Providing an Investigator's Brochure covering the chemical, pharmaceutical, toxicological, pharmacological, and clinical (including previous and ongoing trials) information and data for the investigational product.
4) Designing a clinical trial protocol jointly with the investigator. Signing the trial protocol and contract agreed upon by both parties.
5) Providing the investigator with an investigational product and a comparator that are easy to identify, correctly coded, and specially labeled, while guaranteeing the quality of the investigational product and the comparator. Packaging and storing the investigational product properly as required by the trial protocol. Establishing a management system and recording system for the investigational product.
6) Appointing qualified monitors who are accepted by the investigator.
7) Establishing a quality control and quality assurance system for the clinical trial, and organizing audits for the clinical trial to ensure its quality.
8) Working with the investigator to promptly study the SAEs that have occurred and taking necessary measures to ensure the safety and rights of the subjects. Reporting the SAEs to the drug regulatory authorities and health administrative departments in a timely manner.
9) Submitting a final report of the trial to the CFDA.
10) Purchasing the liability insurance for this drug clinical trial. Providing comprehensive medical coverage for the subjects of the clinical trial, and bearing the cost of the treatment and corresponding financial compensation for the subjects experiencing injuries or deaths

associated with the trial. Providing the investigator with legal and economic guarantees, except for those caused by medical malpractice.

10.1.15.3 Access to Source Data

The CRA is a primary liaison between the sponsor and the investigator. The CRA will fulfill all monitoring responsibilities to monitor this clinical study in accordance with GCP. The CRA will establish and maintain regular contact between the investigator and the sponsor.

The CRA will conduct regular clinical monitoring according to all relevant regulatory requirements and standards, or visit the study site depending on actual situation, push the progress of the clinical trial, check and verify if all data records and reports, and eCRF entries are correct and complete, and consistent with the source data, and ensure that the clinical trial is performed according to the clinical trial protocol; the investigator shall actively assist the CRA in these processes.

10.2 Appendix 1: Common Terminology Criteria for Adverse Events

This study will report AE using CTCAE v5.0 can be downloaded from the home page of the Cancer Therapy Evaluation Program (CTEP). CTCAE v5.0 shall be used in all relevant study sites. The URL is as follows:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

10.3 Appendix 2-1: Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

The following is the Response Evaluation Criteria in Solid Tumors RECIST Version 1.1. For more details, please refer to the English version at http://ctep.cancer.gov/protocolDevelopment/docs/ recist_guideline.pdf.

Method

- Currently, CT and MRI are the best reproducible methods used for assessing the response of selected target lesions. The lesion on the CT scan is measured according to the following assumption: CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be at least twice the slice thickness. The use of MRI to assess diseases throughout the entire study is acceptable.
- Through the entire trial, the same assessment method and the same technique are used to characterize each identified and reported lesion.
    - An ultrasound diagnosis shall not be used to measure objective tumor response or disease progression. For this study protocol, cross sectional imaging techniques (CT or MRI) are used to assess complete responses, partial response, or stable disease. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) examination is not suitable for assessing tumor response. It is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of disease progression. To determine progressive disease (PD), new lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

If the investigator decides to use combined PET-CT, the CT portions of PET-CT shall not be substituted for dedicated CT examination required by this study protocol to complete the RECIST measurement, unless the research institute may confirm that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Cytology and histology can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and disease progression.

The definitions of "measurable" and "non-measurable" tumors:

All measurements should be recorded in metric notation, using rulers or calipers. Measurement results shall be recorded in a single dimension. At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

- Measurable: The tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm). When the CT scan slice thickness is greater than 5 mm, the longest diameter of the measurable lesion shall be at least 10 mm or twice the slice thickness. Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan.
- Non-measurable: All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions, that are characterized as non-target lesions. Lesions considered truly non-measurable include: bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules and tangible lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. Lesions which cannot be accurately measured with calipers should be recorded as non-measurable.

Special considerations regarding lesion measurability:

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components (that can be evaluated by cross sectional imaging techniques such as CT or MRI) can be considered as

measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic lesions: Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions. "Cystic lesions" is thought to represent cystic metastases that can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Baseline (i.e., before treatment) documentation of "target" and "non-target" lesions.

During treatment, a maximum of five 5 target lesions are selected for measurement (a maximum of two lesions per organ). Target lesions shall be selected according to their size and the appropriateness of reproducible repeated measurements using imaging techniques or clinical means.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- All other lesions (or affected sites; including any measurable lesions or pathological lymph nodes not selected as target lesions) shall be identified as non-target lesions. Non-target lesions shall be recorded and qualitatively assessed during treatment. Measurements are not required, and these lesions should be followed as "present", "absent", or in rare cases "unequivocal progression".
- Bone lesions: Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. If a sign or symptom indicative of bone metastases is present, a bone scan, MRI, CT, PET, PET/CT, or X-ray scan shall be performed. For subjects who are positive for bone scans or PET scans, another imaging technique (e.g., X-ray, CT, or MRI) must be used to confirm bone metastasis.

Response criteria

A subject's tumor response is assessed based on the response for target and non-target lesions, as well as the appearance of new lesions and disappearance of old lesions.

Table 10: Evaluation of Target Lesions

*Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10 mm.
*Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
*Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
*Stable Disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while in study.
Not Applicable (NA):	No target lesions are identified at baseline.
Not Evaluable (NE):	The scan is not completed, the scan result is incomplete, or the scan is not evaluated due to poor quality of the scan at the time point chosen for the evaluation of target lesions.

*Diameter to be used:
For lymph node lesions: the shortest axis
For non-lymph node lesions: the sum of longest diameters

Once the study is started, the following rule will be adopted: If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If the size of the lesion increases to 5 mm or more in one direction, their actual diameter shall be recorded. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm in study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. In order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Table 11: Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis)
Non-CR/non-PD:	Persistence of one or more non-target lesion(s)
Progressive Disease (PD):	Appearance of one or more new lesions, or if the original non-target lesions show suspicious progression.
Not Applicable (NA):	No non-target lesions are identified at baseline.
Not Evaluable (NE):	The scan is not completed, the scan result is incomplete, or the scan is not evaluated due to poor quality of the scan at the time point chosen for the evaluation of non-target lesions.

When the patient also has measurable disease, in this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease. Even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. When the patient has only non-measurable disease, the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease (which is equivalent to a 20% increase in the sum of diameters in all measurable lesions).

Evaluation of best overall response

The status of the overall response of subjects at various time points is calculated as follows:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = in evaluable

Time point response of patients with non-target disease only.

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
NE	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = in evaluable

A "Non-CR/Non-PD" is preferred over "stable disease" for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Special notes on response assessment

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". In this case, it is not possible at this time to use " disease progression" as an overall objective response of the tumor. Every effort should be made to document objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or disease progression is objectively documented (taking as reference for disease progression the smallest measurement recorded in study).

10.4 Appendix 2-2: iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics

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iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics

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For the **EORTC RECIST data warehouse** see www.eortc.org/RECIST

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Abstract

Tumours respond differently to immunotherapies compared with chemotherapeutic drugs, raising questions about the assessment of changes in tumour burden—a mainstay of evaluation of cancer therapeutics that provides key information about objective response and disease progression. A consensus guideline—iRECIST—was developed by the RECIST working group for the use of modified Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) in cancer immunotherapy trials, to ensure consistent design and data collection, facilitate the ongoing collection of trial data, and ultimate validation of the guideline. This guideline describes a standard approach to solid tumour measurements and definitions for objective change in tumour size for use in trials in which an immunotherapy is used. Additionally, it defines the minimum datapoints required from future trials and those currently in development to facilitate the compilation of a data warehouse to use to later validate iRECIST. An unprecedented number of trials have been

done, initiated, or are planned to test new immune modulators for cancer therapy using a variety of modified response criteria. This guideline will allow consistent conduct, interpretation, and analysis of trials of immunotherapies.

Introduction

Changes in tumour burden (termed response) are often used as surrogates of survival or quality of life;[1] consequently, validated and consistent criteria for defining response to treatment are crucial. In 2000, the Response Evaluation Criteria in Solid Tumours (RECIST) working group simplified the 1981 WHO response criteria[2] after validation in a large data warehouse.[3] In 2009, RECIST was refined to RECIST version 1.1.[4] The RECIST working group ensures that RECIST undergoes continuous testing, validation, and updates.[5–7]

Immune modulators are one of the most important classes of new anticancer therapeutics.[8–10] Cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), and programmed death ligand-1 (PD-L1) pathways are the most intensively studied,[11–17] and drugs that are active in these pathways have, since 2011, received marketing authorisation (for some drugs the authorisation is conditional, pending the completion of other studies) for melanoma, lung, bladder, renal, and head and neck cancer.[18–23] The novel mechanism of action of these drugs, with immune and T-cell activation, is postulated to lead to unusual patterns of response that resemble tumour flare but are more pronounced and more frequent than previously described responses. In early trials of immune-based therapeutics in melanoma, investigators described unique response patterns, termed pseudoprogression. Some patients whose disease met the criteria for disease progression based on traditional response criteria such as RECIST (an increase in the sum of measures of target lesions, unequivocal increase in non-target disease, or the appearance of new lesions) were noted to have late but deep and durable responses.[24–28] In 2009, modified response criteria based on WHO criteria (which include the collection of bidimensional measurements of target lesions) were proposed—the immune-related response criteria (irRC).[29] The major modification involved the inclusion of the measurements of new target lesions (each must be at least 5 × 5 mm in size; with a maximum of ten visceral lesions in total, up to five new lesions per organ, and five new cutaneous lesions) into disease assessments. In 2013, researchers published revised irRC using unidimensional measurements based on the original RECIST.[30] Subsequent recommendations, some published in abstract form, seem to incorporate RECIST 1.1 recommendations.[31–33] These recommendations are often referred to as irRECIST, but have not always been consistently applied, leading to concerns about the comparability of data and results across trials, difficulty with pooling databases, and poor clarity regarding whether new lesions were measured, and if so, how many were captured, and whether measures were incorporated into tumour burden. Recent trials (since 2010) have generally used RECIST-based immune criteria to assess responses to immunotherapies.

Because of the need to standardise and validate response criteria, the RECIST working group prospectively planned to create a warehouse of data from trials of immunotherapeutics to test and validate RECIST 1.1 and suggest modifications if required. During the planning

and initial collection of the immunotherapeutic warehouse, it was apparent that most trials testing these drugs have typically used RECIST 1.1 to define the primary and secondary efficacy-based endpoints, and reserved irRC or their modified definition of RECIST for exploratory endpoints.[31,32] Additionally, substantial variability in which criteria were used was seen across clinical trials within pharmaceutical companies and cooperative groups, leading to serious concerns about interpretation of pooled datasets. Finally, most trials that used immune-modified criteria used independent imaging review by a commercial entity for those criteria, rather than investigator assessments. We think that response criteria should be applicable across all cancer clinical trials, including those done in the academic sector, where costly independent review is not feasible.

On the basis of these observations, the RECIST working group decided to develop a guideline for the use of a modified RECIST to ensure consistent design and data collection that would facilitate the ongoing collection of clinical trial data and ultimate validation, if indicated, of a modified RECIST 1.1 for immune-based therapeutics (termed iRECIST). These guidelines are not intended to define or guide clinical practice or treatment decisions, but rather to provide a consistent framework for the management of data collected in clinical trials of immune-based therapies. Treatment decisions rest with the patient and their health-care team.

Terminology

iRECIST is based on RECIST 1.1. Responses assigned using iRECIST have a prefix of “i” (ie, immune)—eg, “immune” complete response (iCR) or partial response (iPR), and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD) to differentiate them from responses assigned using RECIST 1.1. Similar nomenclature is used for stable disease (iSD). New lesions are assessed and subcategorised into those that qualify as target lesions (new lesion, target) or non-target lesions (new lesion, non-target).

Development of the guideline

The RECIST working group formed a subcommittee and held a series of conference calls and face-to-face meetings in 2015 and 2016 to discuss plans for the development and validation of iRECIST (figure 1) and to review existing approaches to assess response in immune modulator trials, and also to identify points of consensus and items that needed further discussion. Members of the subcommittee included clinical, statistical, and imaging experts in methodology and immunotherapy, representatives from the pharmaceutical companies developing immunotherapeutics, and key regulatory authorities (appendix p 1). On June 2, 2016, a formal meeting was held in Chicago (IL, USA), with invited presentations from regulatory authorities, pharmaceutical companies with immune modulator drugs in development, and academic groups, followed by a structured discussion. Before the meeting, the 52 invited participants were polled to enable the identification of questions that needed to be addressed, as well as the response criteria routinely used by participants. Ten respondents provided responses before the meeting (including some pooled responses) and all eight presenters identified additional areas of interest in their presentations. After review and discussion during the meeting, the group identified a list of

important questions to be addressed by iRECIST (panel 1). Notably, all participants confirmed that RECIST 1.1 was used for primary endpoints, with immune-modified response criteria being used in an exploratory manner, with very few exceptions; in one instance, immune-modified criteria were used as a coprimary endpoint. The most commonly used immune-modified criteria were variations of irRECIST. There was more variability in independent imaging review and the period of time during which response data were collected after RECIST 1.1 progression or cessation of protocol therapy. Further calls and meetings were held to develop and plan the full validation of iRECIST (figure 1).

iRECIST

The continued use of RECIST 1.1 is recommended to define whether tumour lesions, including lymph nodes, are measurable or non-measurable, as well as for the management of bone lesions, cystic lesions, and lesions with previous local treatment (eg, radiotherapy; table 1). Similarly, no changes have been made to the recommendations regarding the method of measurement, although clinical examination and chest radiograph are rarely used, with the availability of more modern imaging techniques (eg, CT scans and MRI). The principles used to establish objective tumour response are largely unchanged from RECIST 1.1, but the major change for iRECIST is the concept of resetting the bar if RECIST 1.1 progression is followed at the next assessment by tumour shrinkage.

iRECIST defines iUPD on the basis of RECIST 1.1 principles; however, iUPD requires confirmation, which is done on the basis of observing either a further increase in size (or in the number of new lesions) in the lesion category in which progression was first identified in (ie, target or non-target disease), or progression (defined by RECIST 1.1) in lesion categories that had not previously met RECIST 1.1 progression criteria. However, if progression is not confirmed, but instead tumour shrinkage occurs (compared with baseline), which meets the criteria of iCR, iPR, or iSD, then the bar is reset so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment for iCPD to be assigned. If no change in tumour size or extent from iUPD occurs, then the timepoint response would again be iUPD. This approach allows atypical responses, such as delayed responses that occur after pseudoprogression, to be identified, further understood, and better characterised (tables 1–3, figure 2, appendix pp 2–4). Sample case record forms and protocol sections are included in the appendix pp 5–19. In the next few paragraphs, we only briefly summarise sections of RECIST 1.1 that are unchanged; readers should refer to RECIST 1.1 for full descriptions.[4]

Assessment of target, non-target, and new lesions

Most RECIST 1.1 recommendations are unchanged for timepoint response, including the management of lymph nodes, lesions that become too small to measure, lesions that split or coalesce, and the definition of complete response, partial response, stable disease, and progressive disease. Each timepoint response is based on the assessment of target lesions, non-target lesions, and new lesions.

For target lesions, iCR, iPR, and iSD can all be assigned after iUPD has been documented, as long as iCPD was not confirmed. iUPD is defined by RECIST 1.1 criteria for progressive

disease; iUPD can be assigned multiple times as long as iCPD is not confirmed at the next assessment. Progression is confirmed in the target lesion category if the next imaging assessment after iUPD (4–8 weeks later) confirms a further increase in sum of measures of target disease from iUPD, with an increase of at least 5 mm. However, the criteria for iCPD (after iUPD) are not considered to have been met if complete response, partial response, or stable disease criteria (compared with baseline and as defined by RECIST 1.1) are met at the next assessment after iUPD. The status is reset (unlike RECIST 1.1, in which any progression precludes later complete response, partial response, or stable disease). iCR, iPR, or iSD should then be assigned; and if no change is detected, then the timepoint response is iUPD.

The assessment of non-target lesions at each timepoint follows similar principles. iUPD (but not iCPD) can have been documented before iCR or when the criteria for neither CR nor PD have been met (referred to as non-iCPD/non-iUPD) and can be assigned several times, as long as iCPD was not confirmed. iUPD is defined by RECIST 1.1 criteria; however, iUPD can be assigned multiple times as long as iCPD is not confirmed at the next assessment. Progressive disease in the non-target lesion category is confirmed if subsequent imaging, done 4–8 weeks after iUPD, shows a further increase from iUPD. The criteria for iCPD are not judged to have been met if RECIST 1.1 criteria for complete response or non-iCR/non-iUPD are met after a previous iUPD. The status is reset (unlike RECIST 1.1) and iCR, or non-iCR/non-iUPD is assigned; if no change is detected, the timepoint response is iUPD.

RECIST 1.1 defines the appearance of new malignant lesions as denoting true disease progression, providing that other lesions (artefacts or benign intercurrent disease) are appropriately assessed and discounted if not malignant. These principles of RECIST 1.1 remain useful and clearly identify the management of new lesions that are considered to be potentially artefactual: “If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up assessment will clarify whether it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan”.[4]

However, many aspects of new lesion assessment are unique to iRECIST. If a new lesion is identified (thus meeting the criteria for iUPD) and the patient is clinically stable, treatment should be continued. New lesions should be assessed and categorised as measurable or non-measurable using RECIST 1.1 principles. Five lesions (no more than two per organ) should be measured and recorded as a new lesion target, but should not be included in the sum of measures of the original target lesions identified at baseline (appendix p 17). Other measurable and non-measurable lesions are recorded as new lesion non-target. Trialists might choose to measure and record more than five new lesions for research purposes, but this method is not believed to be practical for general use. New lesions do not need to meet the criteria for new lesion target to result in iUPD (or iCPD); new lesion non-target can also drive iUPD or iCPD. Progressive disease is confirmed (iCPD) in the new lesion category if the next imaging assessment, done at 4–8 weeks after iUPD, confirms additional new lesions or a further increase in new lesion size from iUPD (sum of measures increase in new lesion target ≥5 mm, any increase for new lesion non-target).

Notably, if iUPD criteria were met on the basis of progression in the target or non-target disease, or the appearance of new lesions, then RECIST 1.1-assigned progression in another lesion category in the confirmatory scan also confirms iCPD.

Continued treatment after iUPD

The existing literature describes pseudoprogression as an increase in the size of lesions, or the visualisation of new lesions, followed by a response, which might be durable. Although well described, differentiating transient pseudoprogression from true progression, potentially requiring a change in therapy, can be challenging. Although early discontinuation of an effective drug is not desirable, continued long-term treatment with a non-effective drug past true progression might delay the initiation of potentially effective salvage therapy.

We recommend that clinical trials in which treatment beyond initial RECIST 1.1-defined progression (ie, iUPD) is permitted should only allow patients who are clinically stable to continue on treatment until the next assessment (≥4 weeks later); this next imaging assessment should be no longer than 8 weeks later, to ensure that patients remain fit for salvage therapies. A longer timeframe before the next assessment might be reasonable if pseudoprogression is well described in the tumour type (eg, melanoma treated with a CTLA4 inhibitor), especially if no effective salvage therapies are available (eg, *BRAF* wild-type melanoma) but should be justified in the trial protocol. All decisions regarding continuation or discontinuation of therapy should be made by the patient and their health-care provider; iRECIST describes what data are to be collected, submitted, and analysed in clinical trials of immune-based therapies.

An assignment of clinical stability requires that no worsening of performance status has occurred, that no clinically relevant increases in disease-related symptoms such as pain or dyspnoea occur that are thought to be associated with disease progression (these symptoms are generally understood to mean a requirement for increased palliative intervention), and that no requirement for intensified management of disease-related symptoms exists, including increased analgesia, radiotherapy, or other palliative care.

The imaging findings and the recommendation to continue with treatment despite iUPD should be discussed with the patient before a decision is made about whether or not to continue therapy. Patients who have iUPD and are not clinically stable should be designated as not clinically stable in the case report form. This designation will allow the best overall response to be calculated and the date of iUPD to be used in estimates of progression-free survival.

If the confirmatory scan confirms iCPD, but the investigator or patient believes that continued treatment is appropriate, imaging should continue and data should be collected to allow further elucidation of tumour growth dynamics with immune modulators. For the same reason, and if feasible, even patients who discontinue therapy for iCPD are recommended to continue to have disease assessments until they start other systemic or local therapies.

Timepoint and best overall response

Although the principles of the assignment of the timepoint response and best overall response closely follow RECIST 1.1, and reflect assessment of target and non-target lesions as well as the presence of new lesions, the possibility of pseudoprogression adds complexity (tables 1–3, panel 2, appendix pp 2–4). The timepoint response is calculated using the response assigned for each category of lesion (as for RECIST 1.1), but takes into account the last timepoint response.

The algorithm for patients with no previous iUPD is identical to RECIST 1.1. For patients with iUPD at the last timepoint response, the next timepoint response is dependent on the status of all lesions, including target, non-target, new lesion target, and new lesion non-target; on whether any increase in size has occurred (either a further increase in size or a sufficient increase to assign a new iUPD if the criteria were not previously met); or the appearance of additional new lesions.

For iRECIST, the best overall response (iBOR) is the best timepoint response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. iUPD will not override a subsequent best overall response of iSD, iPR, or iCR (tables 1–3, appendix pp 2–4), meaning that iPR or iSD can be assigned (timepoint response or iBOR) even if new lesions have not regressed, or if unequivocal progression (non-target lesions) remains unchanged, providing that the criteria for iCPD are not met.

Confirmation of response is not required when using RECIST 1.1, except in non-randomised trials, and this approach is also recommended for iRECIST. The duration of iCR and iPR is from the timepoint when the criteria for iCR or iPR are first met, whereas the duration of iSD is still calculated from baseline.

The protocol should establish how missing response assessments will be handled. Assessments that are not done or are not evaluable should be disregarded. For example, an iUPD followed by an assessment that was not done or not evaluable, and then another unconfirmed progressive disease, would be indicative of iCPD. Protocols should clearly specify whether assessments done after protocol therapy is discontinued can be considered in identification of iBOR; it might be reasonable to include assessments done several weeks or months after protocol treatment has been discontinued if late responses are anticipated (such as with a CTLA4 inhibitor) and patients have not received other systemic or local therapies. Protocols should also specify how any new therapy introduced before progression (eg, radiotherapy or surgery) will affect iBOR designation. Other RECIST 1.1 recommendations, including the management of missing assessments, remain unchanged, including requiring that the statistical analysis plan should indicate how missing data or assessments will be addressed in the determination of response and progression.

Frequency of tumour reassessment

In general, follow-up response assessment every 6–12 weeks is recommended for iRECIST, depending on the frequency of treatment visits, as recommended for RECIST 1.1. The protocol should specify which anatomical locations are assessed at baseline and follow-up,

and whether bone scans should be repeated at each response assessment, only to confirm iPR or iCR, or when clinically indicated. For all trials, especially comparative ones, response assessments should be done on a calendar schedule and not be affected by delays in therapy or the requirement for earlier confirmatory scans, which might be done to confirm iUPD or in some trials, to confirm complete or partial response.

Tumour reassessment can be done earlier than originally planned (but only between 4 and 8 weeks after iUPD) to confirm iUPD (or, in non-randomised trials, to confirm iCR or iPR ≥4 weeks after the scan showing complete or partial response). If progression is not confirmed, reassessment should continue as originally planned (ie, if scans were to be done at 8, 16, and 24 weeks, and a scan was done at 12 weeks to confirm response, then the next scans should be done at 16 weeks and 24 weeks, as planned). If patients continue on treatment per protocol after iCPD, assessments should continue to be done, at the same planned schedule, until protocol treatment is discontinued.

Ideally, all imaging done after protocol treatment has been discontinued should continue to be recorded on the case report form until subsequent therapies are initiated, as the protocol and informed consent document permit. These data will allow further refinement of iRECIST.

Statistical and protocol considerations

The event date to be used for calculation of progression-free survival (iPFS) should be the first date at which progression criteria are met (ie, the date of iUPD) provided that iCPD is confirmed at the next assessment (appendix pp 2–4 and 19). If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, that iUPD date should not be used as the progression event date.

If progression is not confirmed and there is no subsequent iSD, iPR, or iCR, then the iUPD date should still be used in the following scenarios: if the patient stops protocol treatment because they were not judged to be clinically stable, or no further response assessments are done (because of patient refusal, protocol noncompliance, or patient death); the next timepoint responses are all iUPD, and iCPD never occurs; or the patient dies from their cancer. The case report form collects the reason why confirmatory response assessment was not done at any timepoint, such as not clinically stable, centre error, patient refusal, or patient death.

For protocols that permit crossover, or if intermittent schedules are being tested, the protocol should clearly specify whether iUPD or iCPD would be used for a treatment decision leading to crossover and how data subsequent to crossover will be managed and analysed. In general, we suggest that iCPD be used especially for scenarios with immunotherapy in both treatment groups and when pseudoprogression is anticipated.

Adjuvant trials of immune modulators given after curative surgery for melanoma or lung cancer are ongoing (NCT 02437279, 02388906, 02595944, 02504372, and 02273375) but have yet to report their results. Suspected new lesions in the curative setting should always be investigated thoroughly and preferably have a biopsy taken before the designation of

relapse is assigned. If taking a biopsy sample is not technically feasible, then it would seem to be reasonable to follow the principles of iRECIST, with a follow-up scan to confirm relapse in patients who are clinically stable.

The collection of anonymised imaging (even if centralised blinded review of imaging studies is not planned) is recommended for all studies using an imaging-based endpoint (ie, response or progression-free survival) if feasible. Although the iRECIST guideline requires the recording of the measurements of up to five new lesions, it might eventually be necessary to record additional lesions to obtain a more precise estimate of progression. Central collection of images will allow further assessment by an independent radiologist if necessary. If real-time central review is planned, the protocol should clearly explain how treatment decisions will be made.

We recommend that phase 3 clinical trials continue to incorporate both RECIST 1.1 and iRECIST (table 1) and that RECIST 1.1 should continue to be used to define the primary efficacy outcomes (progression-free survival, disease progression, and best overall response). Exploratory analyses using the iPD date (ie, the first date of iUPD that is subsequently confirmed) can be defined in the statistical analysis plan. Early-phase trials can consider using iRECIST as the primary criteria. The protocol should carefully explain which will be the primary criteria used to assess response, and which would be exploratory. This information is especially important for trials that compare an immune modulator treatment with a non-immune modulator treatment.

Discussion: next steps and validation

Immunotherapeutics are a major advance in the treatment of an escalating number of cancers. The increasing testing and use of these drugs in multiple clinical settings, including adjuvant, first, second, and subsequent lines of therapy will require the use of progression-based endpoints. RECIST 1.1 might not always adequately capture the unique patterns of response that have been well described in clinical trials of these drugs in a low proportion of patients, typically reported as 10% or less, mainly in melanoma studies.[32–34] The true frequency in trials of other malignancies (including non-small-cell lung cancer) is unclear because most trials have reported RECIST 1.1-based response rates,[35] but might be less common based on anecdotal reports. Similarly, whether this pattern is unique to drugs active in the CTLA4–PD-1–PD-L1 pathway is currently unknown. Trials testing immunotherapeutics in combination with standard therapies, especially when they are compared with these standard therapies alone, further confound the assessment of progression-based endpoints.

RECIST 1.1 already addresses the management of equivocal progression, including suspected new lesions, which might explain, at least in part, the continued use of RECIST 1.1 to define response-based primary endpoints. RECIST 1.1 deals with mainly technical differences in scans that give the appearance that new lesions might have developed, or the concept of the isodense lesion at baseline that becomes more visible after the start of therapy since it becomes internally more necrotic as opposed to a true new lesion. However, the

intention was never to use those recommendations to manage pseudoprogression described with immune modulators.

Although modified response criteria have been used, a formal guideline is clearly needed, with robust plans for prospective testing and consistent data collection and validation. Trials have not always been consistent in the definition of the response criteria to be used, have used trial-specific modifications of response criteria in which new lesion measurements can or cannot be included in the assessment of response, and response assessments after progression defined by RECIST 1·1 are not always done. Those data are crucial to understand the dynamics of tumour response to immunotherapeutics, including whether immunotherapeutics with different mechanisms of action have varying effects.

Although some progress has been made in understanding tumour dynamics with immunotherapeutics, progress in this area has undoubtedly been limited by reluctancy toward data sharing across trials, companies, and immunotherapeutics. Publications have been based on trials done by individual pharmaceutical companies or commercial organisations. In the development of this guideline, virtually all major pharmaceutical companies developing immunotherapeutics participated and have shared their experiences, protocols, response criteria, and, most importantly, their data. The iRECIST team also included members of the European Medicines Agency and the US Food and Drug Administration.

Although this guideline is consensus based, it is not yet validated because the data warehouse is still being created with initial trial data already in place. The guideline includes all available knowledge on response dynamics, allowing appropriate management of true pseudoprogression, but importantly, it also safeguards patients: although pseudoprogression is now well described, it still only occurs in fewer than one in ten patients. Treatment past radiographic progression might be appropriate only in a small number of patients, and the continuation of treatment past true progression could reduce subsequent effective therapies if the patient is no longer fit enough to tolerate any further treatment.

iRECIST requires the confirmation of progression to rule out or confirm pseudoprogression. Although this recommendation is in keeping with that of RECIST 1.1 to continue treatment and repeat imaging in the case of a mixed response or equivocal findings, if pseudoprogression is common, patients might be exposed to a higher risk (of continuing ineffective therapy or increasing exposure to radiotherapy) or cost (for the potentially ineffective therapy or the costs of imaging). We recommend that these criteria are used for clinical trial protocols rather than to guide clinical practice. Treatment beyond RECIST 1.1-based progression should be considered only in carefully selected scenarios in which the patient is stable (or improving) symptomatically and if there is just a short period remaining before reassessment.

Although at first glance the recommendation to collect measurements of new lesions as defined in this guideline seems onerous, the collection of these measurements and the recording of both RECIST 1.1 and iRECIST for timepoint response and best overall response have several benefits. The association between the site of the new lesion and

progression-free survival and the value of adding new lesion measurements to the sum of measures can be explored. Continuing to record RECIST 1.1 allows comparison with reported immunotherapy trials that have used RECIST 1.1, as well as chemotherapy trials, while also allowing treatment past progression and collecting data that will allow further testing and validation of iRECIST. Differences in trial outcomes using RECIST 1.1 versus iRECIST could occur, and the interpretation will be informative. Our proposed plan will enable identification of such situations, and hopefully clarification of the underlying mechanisms. Additionally, in the future, quantification of the differences in outcome estimation between RECIST 1.1 and iRECIST will be possible, enabling better informed decisions for future changes to RECIST guidelines.

This strategy will also be useful for trials comparing immunotherapy-based with non-immunotherapy-based therapeutics. RECIST 1.1 and iRECIST should yield almost identical results for non-immunotherapy treatments, based on the RECIST warehouses; whereas an immune modulator warehouse and associated sensitivity analysis of endpoints will enable the quantification of potential added benefit for the immunotherapy component. Although comparison of iRECIST in such situations incorporates an element of bias by construction, confirmation and validation of the guideline by overall survival results might gain additional importance.

Our recommendation for the design of randomised studies planned for licensing applications is to continue to use RECIST 1.1 as the primary criteria for response-based endpoints. iRECIST should be regarded as exploratory in such trials, although earlier phase trials might consider using primarily iRECIST.

The creation of a data warehouse is underway and updates are available from EORTC where the warehouse is held. Meanwhile the implementation of this guideline, and the continued sharing of anonymised, patient-level data will allow the formal validation of iRECIST, ensuring that response-based guidelines remain robust and enable the rapid and robust future development of new cancer therapeutics to improve treatments for patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Kim C, Prasad V. Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival: an analysis of 5 years of US Food and Drug Administration approvals. JAMA Intern Med. 2015; 175:1992–94. [PubMed: 26502403]
2. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer. 1981; 47:207–14. [PubMed: 7459811]
3. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000; 92:205–16. [PubMed: 10655437]
4. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1·1). Eur J Cancer. 2009; 45:228–47. [PubMed: 19097774]
5. Liu Y, Litière S, de Vries EG, et al. The role of response evaluation criteria in solid tumor in anticancer treatment evaluation: results of a survey in the oncology community. Eur J Cancer. 2014; 50:260–66. [PubMed: 24239447]
6. Schwartz LH, Seymour L, Litière S, et al. RECIST 1.1—standardisation and disease-specific adaptations: perspectives from the RECIST working group. Eur J Cancer. 2016; 62:138–45. [PubMed: 27237360]
7. Schwartz LH, Litière S, de Vries E, et al. RECIST 1·1—update and clarification: from the RECIST committee. Eur J Cancer. 2016; 62:132–37. [PubMed: 27189322]
8. Brahmer J, Reckamp KL, Baas P, Crinò L, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015; 373:123–35. [PubMed: 26028407]
9. Pardoll, Drew M. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012; 12:252–64. [PubMed: 22437870]
10. Sidaway P. Bladder cancer: atezolizumab effective against advanced-stage disease. Nat Rev Urol. 2016; 13:238.
11. Holt GE, Podack ER, Raez LE. Immunotherapy as a strategy for the treatment of non-small cell lung cancer. Therapy. 2011; 8:43–54. [PubMed: 21359153]
12. Sharma P, Wagner K, Wolchok JD, Allison JP. Novel cancer immunotherapy agents with survival benefit: recent successes and next steps. Nat Rev Cancer. 2011; 11:805–12. [PubMed: 22020206]
13. Antonia S, Goldberg SB, Balmanoukian A, et al. Safety and antitumor activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. Lancet Oncol. 2016; 3:299–308.
14. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015; 372:2006–17. [PubMed: 25891304]
15. Reck M, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Ann Oncol. 2013; 24:75–83. [PubMed: 22858559]
16. Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small cell lung cancer: results from a randomized, double-blind, multi-center phase II study. J Clin Oncol. 2012; 30:2046–54. [PubMed: 22547592]
17. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015; 373:23–34. [PubMed: 26027431]
18. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010; 363:711–23. [PubMed: 20525992]
19. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Eng J Med. 2012; 366:2443–54.
20. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015; 373:1627–39. [PubMed: 26412456]
21. Garon EB, Rizvi N, Hui R, et al. Pembrolizumab for the treatment of non-small cell lung cancer. N Engl J Med. 2015; 372:2018–28. [PubMed: 25891174]

22. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016; 387:1909–20. [PubMed: 26952546]
23. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015; 373:1803–13. [PubMed: 26406148]
24. Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via CTLA-4 and PD-1 pathways. Immunol Rev. 2008; 224:166–82. [PubMed: 18759926]
25. Fife BT, Pauken KE, Eagar TN, et al. Interactions between PD-1 and PD-L1 promote tolerance by blocking the TCR-induced stop signal. Nat Immunol. 2009; 10:1185–92. [PubMed: 19783989]
26. Iwai Y, Ishida M, Tanaka Y, et al. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA. 2002; 99:12293–97. [PubMed: 12218188]
27. Tarhini AA. Tremelimumab: a review of development to date in solid tumors. Immunotherapy. 2013; 5:215–29. [PubMed: 23444951]
28. Hoos A, Parmiani G, Hege K, et al. A clinical development paradigm for cancer vaccines and related biologics. J Immunother. 2007; 30:1–15. [PubMed: 17198079]
29. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009; 15:7412–20. [PubMed: 19934295]
30. Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013; 19:3936–43. [PubMed: 23743568]
31. Bohnsack O, Ludajic K, Hoos A. Adaptation of the immune-related response criteria: irRECIST. Ann Oncol. 2014; 25(suppl 4):iv361, iv372.
32. Hodi FS, Hwu WJ, Kefford R, et al. Evaluation of immune-related response criteria and RECIST v1·1 in patients with advanced melanoma treated with pembrolizumab. J Clin Oncol. 2016; 34:1510–17. [PubMed: 26951310]
33. Chiou VL, Burotto M. Pseudoprogression and immune-related response in solid tumors. J Clin Oncol. 2015; 33:3541–43. [PubMed: 26261262]
34. Kurra V, Sullivan RJ, Gainor JF, et al. Pseudoprogression in cancer immunotherapy: rates, time course and patient outcomes. Proc Am Soc Clin Oncol. 2016; 34 abstr 6580.
35. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016; 375:1823–33. [PubMed: 27718847]

Panel 1: **Key questions identified by the RECIST working group**

- How to define the date of progression in scenarios in which initial progression by RECIST 1.1 is followed by response and later progression
- How to define best overall response when initial progression is established with RECIST 1.1
- How to manage response and progression in trials comparing standard non-immunotherapy drugs against immunotherapeutics
- Whether or not progression should be confirmed with a second scan; and if so, which timepoint denotes the date of progression?
- New lesions: when to measure, how many to measure, and whether all should be measured at each subsequent assessment
- Optimal timing of frequency of response assessment
- How to manage therapeutic interventions such as surgery or radiotherapy after response

Panel 2: Key principles to be considered

- If the criteria for iUPD have never been met, principles follow RECIST 1.1
- However, if the criteria for iUPD have been met, the next timepoint response could be:
- iUPD: no change noted in any category of lesion
- iSD, iPR, or iCR. Here, iUPD (followed by iCPD) should occur again
- iCPD, if the category in which iUPD was met at the last timepoint response shows a further increase in tumour burden as evidenced (as applicable) by a ≥5 mm increase in sum of measures of target or new target lesions, further increase in non-target or new non-target lesions, or an increase in the number of new lesions

iCPD of a category which did not meet criteria for iUPD now meets the criteria for RECIST 1.1 progression Prefix “i” indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iCR=complete response. iCPD=complete progression. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression.

Search strategy and selection criteria

This paper describes a consensus guideline, rather than a formal literature review. However, a database search was done using PubMed in August, 2016, with the following search terms: “immune response criteria” (limited to cancer, clinical trials, and publications in English language; 234 citations), “irRC” (23 citations), and “pseudoprogression” (limited to cancer, clinical trials, and pubications in English language; 39 citations).

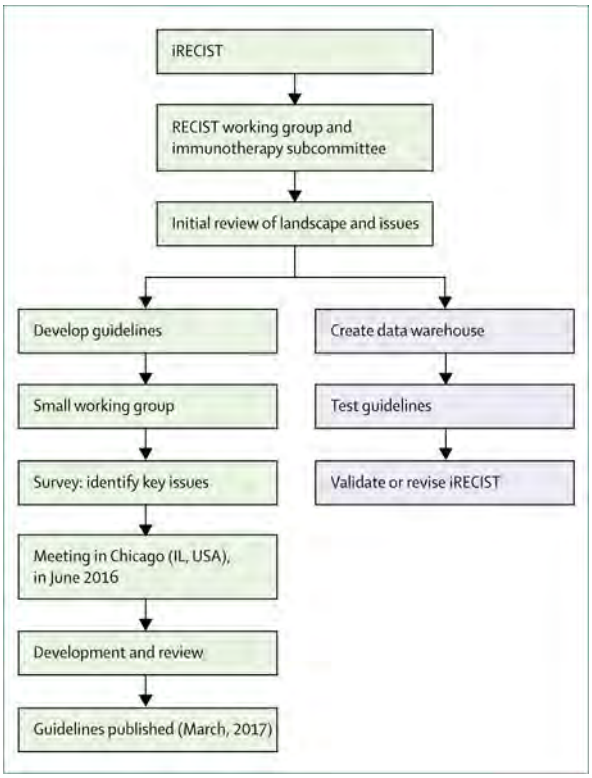


Figure 1. Process for developing and validating iRECIST consensus guidelines

Blue shaded boxes represent steps still in progress. RECIST=Response Evaluation Criteria in Solid Tumours.

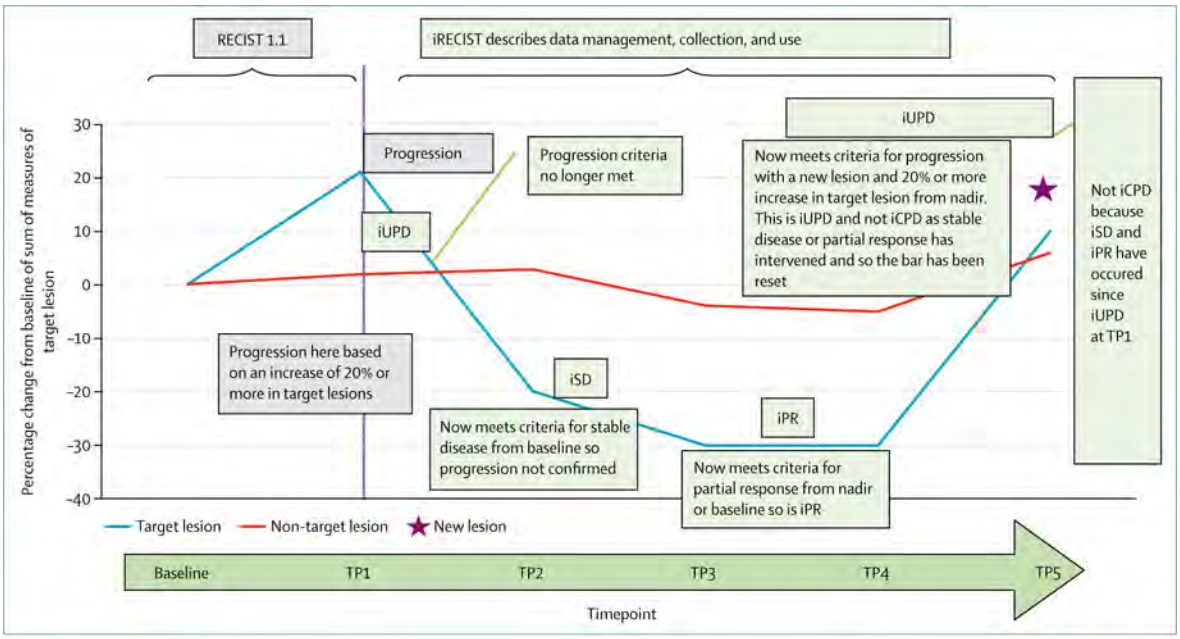


Figure 2. RECIST 1.1 and iRECIST: an example of assessment

Prefix "i" indicates immune responses assigned using iRECIST; others without "i" are confirmed by RECIST 1.1. RECIST=Response Evaluation Criteria in Solid Tumours. iCR=complete response. iCPD=complete progression. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. TP=timepoint.

Table 1

Comparison of RECIST 1.1 and iRECIST

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances —eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

“i” indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Table 2

Assignment of timepoint response using iRECIST

	Timepoint response with no previous iUPD in any category	Timepoint response with previous iUPD in any category*
Target lesions: i CR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures >5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same.

*Previously identified in assessment immediately before this timepoint. “i” indicates immune responses assigned using iRECIST. iCR=complete response. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. non-iCR/non-iUPD=criteria for neither CR nor PD have been met. iCPD=confirmed progression. RECIST=Response Evaluation Criteria in Solid Tumours.

Table 3

Scenarios of assignments of best overall response using iRECIST

	Timepoint response 1	Timepoint response 2	Timepoint response 3	Timepoint response 4	Timepoint response 5	iBOR
Example 1	iCR	iCR, iPR, iUPD, or NE	iCR, iPR, iUPD, or NE	iUPD	iCPD	iCR
Example 2	iUPD	iPR, iSD, or NE	iCR	iCR, iUPD, or NE	iCR, iPR, iSD, iUPD, iCPD, or NE	iCR
Example 3	iUPD	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, NE, or iCPD	iPR, iSD, iUPD, NE, or iCPD	iPR
Example 4	iUPD	iSD or NE	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, iCPD, or NE	iPR
Example 5	iUPD	iSD	iSD, iUPD, or NE	iSD, iUPD, iCPD, or NE	iSD, iUPD, iCPD, or NE	iSD
Example 6	iUPD	iCPD	Any	Any	Any	iCPD
Example 7	iUPD	iUPD (no iCPD)	iCPD	Any	Any	iCPD
Example 8	iUPD	NE	NE	NE	NE	iUPD

Eight examples are presented for patients with target disease at baseline, but many more scenarios exist following the same principles. Table assumes a randomised study in which confirmation of complete response or partial response is not required. For patients with non-target disease only at baseline, only iCR or non-complete response or non-progression of disease can be assigned at each timepoint (not shown in the table for ease of presentation). “i” indicates immune responses assigned using iRECIST. iBOR=best overall response. iCR=complete response. iPR=partial response. NE=not evaluable. iUPD=unconfirmed progression. iCPD=confirmed progression. iSD=stable disease. RECIST=Response Evaluation Criteria in Solid Tumours.

10.5 Appendix 3: Quality of Life Scale EORTC QLQ-C30, EQ-5D-5L, EORTC QLQ-LC13

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4

11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EQ-5D-5L Health Questionnaire

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

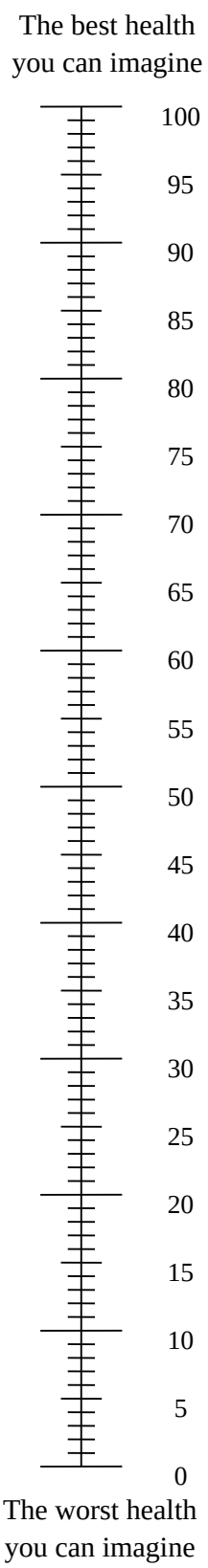
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



EORTC QLQ- LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

10.6 Appendix 4: Eastern Cooperative Oncology Group (ECOG) - Performance Status Scale

Score	ECOG Status
0	Mobility is completely normal, and there is no difference before and after the onset of the disease.
1	Free to walk and engage in light physical activities, including general housework or office work, but not heavy physical activities.
2	Able to walk and independently take care of oneself, but cannot do any work. Able to get up and move around for at least half of the time during the day.
3	Able to only finish some of self-care activities and spend more than half of the time during the day in bed or in a wheelchair.
4	Complete disability. Cannot take care of oneself at all. Totally confined to bed or in a wheelchair.
5	Death

ECOG = Eastern Cooperative Oncology Group

10.7 Appendix 5: Fridericia Correction Formula

Fridericia formula: $QTc=QT/RR^{0.33}$

10.8 Appendix 6: Cockcroft and Gault Formula

The creatinine clearance rate is calculated using the measured value of serum creatinine (unit: mg/dL):

Male: $\frac{(140-\text{age}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72}$

Female: $\frac{(140-\text{age}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72} \times 0.85$

Cited from Cockcroft DW et al. Nephron. 1976; 16(1): 31-41.

The creatinine clearance rate is calculated using the measured value of serum creatinine (unit: μmol/L):

Male: $\frac{(140-\text{age}) \times \text{weight (kg)} \times 1.23}{\text{creatinine (μmol/L)}}$

Female: $\frac{(140-\text{age}) \times \text{weight (kg)} \times 1.23 \times 0.85}{\text{creatinine (μmol/L)}}$

Cited from Cockcroft DW et al. Nephron. 1976;16(1):31-41.

10.9 Appendix 7: Heart Functional Classification of New York Heart Association

Grade	Behavioral Status
Grade I	Physical activities are not restricted. Normal physical activities do not cause excessive fatigue, palpitations or breathing difficulties
Grade II	Physical activities are slightly restricted, and the patient feels comfortable at rest. However, normal physical activities can cause fatigue, palpitations or difficulty breathing
Grade III	Physical activities are significantly restricted. The patient feels comfortable at rest. However, activities lighter than normal physical activities can cause fatigue, palpitations or difficult breathing
Grade IV	Unable to perform any physical activity comfortably. Symptoms of cardiac insufficiency can occur even at rest. Any physical activity can aggravate discomfort.

10.10 Appendix 8: Guidelines for Dose Modification and Treatment for Immune-Related Toxicity

The following is the "NCCN Guidelines for Management of Immunotherapy-Related Toxicities" (2019, v2). For more details, please refer to the original document at https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

AE	Assessment	Grading	Management
Infusion-related reactions			
	• Physical exam • Vital signs • Pulse oximetry • ECG (if chest pain • or sustained tachycardia)	Mild (G1) or Moderate (G2)	• Treat per institutional guidelines • Consider hold or slow the rate of infusion • Continue immunotherapy • Consider premedication with acetaminophen and diphenhydramine with future infusions
		Severe (G3–4)	• Treat per institutional guidelines • Permanently discontinue immunotherapy • There are no data to guide the use of alternate immune checkpoint inhibitors
Dermatologic Adverse Event(s)			
Maculopapular rash	• Total body skin exam, including mucosa • Assess for history of prior inflammatory dermatologic diseases • Consider biopsy if unusual features	Mild (G1)	• Continue immunotherapy • Topical emollient • Oral antihistamine • Treatment with moderate potency topical steroids to affected areas
		Moderate (G2)	• Consider holding immunotherapy • Topical emollient • Oral antihistamine • Treatment with high potency topical steroids to affected areas and/or • Prednisone 0.5–1 mg/kg/day

AE	Assessment	Grading	Management
		Severe (G3–4)	• Hold immunotherapy • Treatment with high potency topical steroids to affected areas • Prednisone 0.5–1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) • Urgent dermatology consultation • Consider inpatient care
Pruritus	• Total body skin exam, including mucosa • Assess for history of prior inflammatory dermatologic diseases	Mild (G1)	• Continue immunotherapy • Oral antihistamine • Treatment with moderate potency topical steroids to affected areas
		Moderate (G2)	• Continue immunotherapy with intensified antipruritic therapy • Oral antihistamine • Treatment with high potency topical steroids to affected areas • Dermatology consultation
		Severe (G3)	• Hold immunotherapy • Oral antihistamine • Prednisone/methylprednisolone 0.5–1 mg/kg/day • Consider GABA agonists (gabapentin, pregabalin) • Consider aprepitant or omalizumab for refractory cases • Urgent dermatology consultation
Bullous dermatitis	Urgent dermatology consultation	Mild (G1)	• Hold immunotherapy • Treatment with high potency topical steroids to affected areas

AE	Assessment	Grading	Management
		Moderate (G2)	• Hold immunotherapy until < G1 • Prednisone/methylprednisolone 0.5–1 mg/kg/day
		Severe (G3) or life-threatening	• Permanently discontinue immunotherapy • Prednisone/methylprednisolone 1–2 mg/kg/day g Inpatient care required • Urgent dermatology, ophthalmology, and urology consultation
Stevens-Johnson Syndrome (SJS) Toxic epidermal necrolysis (TEN)	Urgent dermatology consultation	Severe (G3) or life-threatening	• Permanently discontinue immunotherapy • Prednisone/methylprednisolone 1–2 mg/kg/day • Inpatient care required • Urgent dermatology, ophthalmology, and urology consultation
Gastrointestinal Adverse Event(s)			
Diarrhoea Colitis	• Stool evaluation to rule out infectious aetiology ✓ Nucleic acid amplification tests (NAATs) for GI pathogens/bacterial culture ✓ C. difficile ✓ Ova & parasites; molecular testing for Giardia and Cryptosporidium spp and E. histolytica; consider microsporidia, Cyclosporal/isospora spp ✓ Viral pathogens testing when available	Mild (G1)	• Consider holding immunotherapy • Loperamide or diphenoxylate/atropine • Hydration • Close monitoring
		Moderate (G2)	• Hold immunotherapy • Methylprednisolone 1 mg/kg/day i.v. • No response in 2–3 days: ✓ Increase dose to 2 mg/kg/day ✓ Consider adding infliximab
		Severe (G3–4)	• G3: Discontinue anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity • G4: Permanently discontinue immunotherapy agent responsible for toxicity

AE	Assessment	Grading	Management
	✓ Based on institutional availability, consider lactoferrin/calprotectin • Consider abdominal/pelvic CT with contrast • Consider GI consultation ✓ Colonoscopy or flexible sigmoidoscopy ± esophagogastroduodenoscopy (EGD) with biopsy		• Consider inpatient care for provision of supportive care • Methylprednisolone 2 mg/kg/day i.v. • No response in 2 days: ✓ Continue steroids, consider adding infliximab ✓ If infliximab-refractory, consider vedolizumab
Hepatic Adverse Event(s)			
Transaminitis without elevated bilirubin	• Rule out viral aetiology, disease-related hepatic dysfunction, other drug-induced transaminase elevations • Consider GI evaluation • Ultrasound ✓ If normal ultrasound, consider magnetic resonance cholangiopancreatography (MRCP) ✓ Limit/discontinue hepatotoxic medications (assess acetaminophen, dietary supplement, and alcohol use)	Mild (G1) < 3 × ULN	• Continue immunotherapy, consider holding immunotherapy for concerning lab value trend • Assess transaminases and bilirubin with increased frequency
		Moderate (G2) 3–5 × ULN	• Hold immunotherapy • Monitor liver function tests (LFTs) every 3–5 days • Consider prednisone 0.5–1 mg/kg/day
		Severe (G3) > 5–20 × ULN	• Permanently discontinue immunotherapy • Initiate prednisone 1–2 mg/kg/day • Consider inpatient care • Monitor liver enzymes every 1–2 days • Hepatology consultation • If steroid refractory or no improvement after 3 days, consider adding mycophenolate • Infliximab should not be used for hepatitis
		Life-threatening (G4)	• Permanently discontinue immunotherapy

AE	Assessment	Grading	Management
		> 20 × ULN	• Initiate prednisone/methylprednisolone 2 mg/kg/day • Inpatient care • Monitor liver enzymes daily • Hepatology consultation • Liver biopsy if no contraindications • If steroid refractory or no improvement after 3 days, consider adding mycophenolate • Infliximab should not be used for hepatitis
Grade > 1 transaminitis with bilirubin > 1.5 × ULN (unless Gilbert's syndrome)	• Rule out viral aetiology, disease-related hepatic dysfunction, other drug-induced transaminase elevations • Consider GI evaluation • Limit/discontinue hepatotoxic medications (assess acetaminophen, dietary supplement, and alcohol use)		• Permanently discontinue immunotherapy • Initiate prednisone/methylprednisolone 2 mg/kg/day • Inpatient care • Monitor liver enzymes daily • Hepatology consultation • If steroid refractory or no improvement after 3 days, consider adding mycophenolate • Infliximab should not be used for hepatitis
Pancreatic Adverse Event(s)			
Elevation in amylase/lipase (asymptomatic)	• Assess for signs/symptoms of pancreatitis • If clinical concern for pancreatitis, see acute pancreatitis	Mild Amylase ≤ 3 × ULN and/or Lipase ≤ 3 × ULN	• If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy • Evaluate for pancreatitis ✓ Clinical assessment cc ✓ Consider abdominal CT with contrast ✓ Consider magnetic resonance cholangiopancreatography (MRCP)

AE	Assessment	Grading	Management
			• If evidence of pancreatitis, manage according to pancreatitis algorithm • Consider other causes for elevated amylase/lipase
		Moderate Amylase > 3–5 × ULN and/or Lipase > 3 × ULN	• If isolated elevation of enzymes without evidence of pancreatitis, consider continuing immunotherapy • Evaluate for pancreatitis ✓ Clinical assessment ✓ If persistent moderate to severe amylase and/or lipase elevation, abdominal CT with contrast or MRCP • Consider other causes for elevated amylase/lipase • If evidence of pancreatitis, manage according to pancreatitis algorithm
		Severe Amylase > 5 × ULN and/or Lipase > 5 × ULN	• If isolated elevation of enzymes without evidence of pancreatitis, consider continuing immunotherapy • Evaluate for pancreatitis ✓ Clinical assessment ✓ If persistent moderate to severe amylase and/or lipase elevation, abdominal CT with contrast or MRCP • Consider other causes for elevated amylase/lipase • If evidence of pancreatitis, manage according to pancreatitis algorithm
Acute pancreatitis	• Assess for signs/symptoms of pancreatitis • Abdominal CT with contrast	Mild (G1)	• Consider gastroenterology referral • Manage as per elevation in amylase/lipase
		Moderate (G2)	• Hold immunotherapy

AE	Assessment	Grading	Management
	• Consider MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT		• Prednisone/methylprednisolone 0.5–1 mg/kg/day
		Severe (G3–4)	• Permanently discontinue immunotherapy • Prednisone/methylprednisolone 1–2 mg/kg/day
Endocrine Adverse Event(s)			
Hyperglycaemia Fasting glucose preferred	• New-onset hyperglycaemia < 200 mg/dL and/or • History of type II DM with low suspicion for DKA	• Steroid-related hyperglycaemia or • Preexisting type II DM	• Continue immunotherapy • Monitor serial blood glucose with each dose • Diet and lifestyle modification if needed, medical therapy per institutional guidelines • Consider endocrine consultation if patient is symptomatic and/or glucose is persistently uncontrolled
	• New-onset fasting glucose > 200 mg/dL or • Random blood glucose > 250 mg/dL or • History of type II DM with fasting/random glucose > 250 mg/dL	• Consider new-onset type I DM • Evaluate for DKA if clinically appropriate as per institutional guidelines • Blood pH, basic metabolic panel, urine or serum ketones, beta hydroxybutyrate • C-peptide, if urine or serum ketones/anion gap positive • Consider anti-GAD, anti-islet cell antibodies	Workup negative for DKA • Continue immunotherapy • Monitor serial blood glucose with each dose • Diet and lifestyle modification if needed, medical therapy per institutional guidelines • Consider endocrine consultation if patient is symptomatic and/or glucose is persistently uncontrolled Workup positive for DKA • Hold immunotherapy • Inpatient care • Endocrine consultation • Management of DKA as per institutional guidelines • Insulin as directed by inpatient team and/or endocrinologist
		• $4 \leq TSH < 10$	• Continue immunotherapy

AE	Assessment	Grading	Management
Asymptomatic/subclinical hypothyroidism	• Monitor thyroid-stimulating hormone (TSH), free T4 every 4–6 weeks • If TSH elevated, proceed based on TSH levels as follows or repeat TSH, free T4 in 4–6 weeks	• Patient asymptomatic • Normal free T4	• Continue to monitor thyroid function tests (TFTs)
		• Elevated TSH (> 10) • Normal free T4	• Continue immunotherapy • Consider levothyroxine
		• Normal or low TSH • Low free T4	• See Central hypothyroidism
Clinical, primary hypothyroidism	• Monitor thyroid-stimulating hormone (TSH), free T4 every 4–6 weeks		• Continue immunotherapy • Consider endocrine consultation • Thyroid hormone supplementation • Exclude concomitant adrenal insufficiency (AM cortisol level)
Thyrotoxicosis	• Low or suppressed TSH with high free T4/total T3, consider thyroid peroxidase (TPO) antibody and thyroid-stimulating hormone receptor antibody (TRAb) • Consider endocrine consultation		• Continue immunotherapy if asymptomatic • Consider propranolol (10–20 mg every 4–6 h as needed) or atenolol or metoprolol as needed for symptoms until thyrotoxicosis resolves • Repeat TFTs in 4–6 weeks. ✓ If resolved, no further therapy. ✓ If remains with suppressed TSH, high free T4/total T3, then 4- or 24-h I-123 thyroid uptake/scan to determine if true hyperthyroidism and Graves-like aetiology • Thyrotoxicosis often evolves to hypothyroidism • If TSH is > 10, initiate levothyroxine therapy, oral daily ~1.6 mcg/ kg or 75–100 mcg with goal of getting TSH to reference range or age-appropriate range.
Primary adrenal	• Evaluate cortisol level (AM)		• Endocrine consultation

AE	Assessment	Grading	Management
insufficiency	• Comprehensive metabolic panel (Na, K, CO_2, glucose), renin level		• Endocrine evaluation prior to surgery or any procedure • Hold immunotherapy • Start corticosteroid first before other hormone replacement to avoid adrenal crisis • Steroid replacement ✓ Hydrocortisone 20 mg in AM, 10 mg in PM, then slowly titrating doses down according to symptoms or ✓ Prednisone 7.5 mg or 10 mg starting dose, then reduce to 5 mg daily as appropriate and ✓ Fludrocortisone can be started 0.1 mg every other day; then titrated up or down based on blood pressure, symptoms, lower-extremity oedema, and labs • If hemodynamically unstable, inpatient care and initiate high-dose/stress-dose steroids • Patients with severe symptoms (hypotension) may require additional fluids (e.g., normal saline often > 2 L required) • Patient education regarding stress doses of hydrocortisone for infection, trauma, etc. ✓ Alert bracelet is recommended
Central hypothyroidism	• Evaluate cortisol (AM), FSH, LH, TSH, free T4, DHEA-S • Estradiol testing in women		• Continue immunotherapy • Treat as hypophysitis

AE	Assessment	Grading	Management
	• Testosterone testing in men • Consider MRI of pituitary if confirmed central thyroid/adrenal insufficiency		
Hypophysitis	• Evaluate cortisol (AM), FSH, LH, TSH, • free T4, testosterone in men, oestrogen in premenopausal women • MRI brain ± contrast with pituitary/sellar cuts, if symptomatic		• Consider endocrine consultation • Hold immunotherapy until acute symptoms resolve • If symptomatic, prednisone/methylprednisolone 1–2 mg/kg/day • Hormone replacement as indicated • Patient education regarding stress doses of hydrocortisone for infection, trauma, etc. ✓ Alert bracelet is recommended
Pulmonary Adverse Event(s)			
Pneumonitis		Mild (G1)	• Hold immunotherapy • Reassess in 1–2 weeks ✓ H&P ✓ Pulse oximetry (resting and with ambulation) • Consider chest CT with contrast ✓ Consider repeat chest CT in 3–4 weeks or as clinically indicated for worsening symptoms
		Moderate (G2)	• Hold immunotherapy • Consider infectious workup: ✓ Nasal swab for potential viral pathogens ✓ Sputum culture, blood culture, and urine culture • Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection and malignant lung infiltration

AE	Assessment	Grading	Management
			• Consider chest CT with contrast ✓ Repeat chest CT in 3–4 weeks • Recommend infectious evaluation with institutional immunocompromised panel • Consider empiric antibiotics if infection has not yet been fully excluded • Prednisone/methylprednisolone 1–2 mg/kg/day • Monitor every 3–7 days with: ✓ H&P ✓ Pulse oximetry (resting and with ambulation) • If no improvement after 48–72 h of corticosteroids, treat as Grade 3
		Severe (G3–4)	• Permanently discontinue immunotherapy • Inpatient care • Infectious workup: ✓ Consider that patient may be immunocompromised ✓ Nasal swab for potential viral pathogens ✓ Sputum culture, blood culture, and urine culture • Pulmonary and infectious disease consultation, consider PFT • Bronchoscopy with BAL to rule out infection and malignant lung infiltration • Consider empiric antibiotics if infection has not yet been fully excluded • Methylprednisolone 1–2 mg/kg/day. Assess response within 48 h and plan taper over ≥ 6 weeks

AE	Assessment	Grading	Management
			• Consider adding any of the following if no improvement after 48 h: ✓ Infliximab 5 mg/kg IV, a second dose may be repeated 14 days later at the discretion of the treating provider ✓ Mycophenolate mofetil 1–1.5 g BID then taper in consultation with pulmonary service ✓ Intravenous immunoglobulin (IVIG) 2 g/kg
Renal Adverse Event(s)			
Elevated serum creatinine/ acute renal failure	• Limit/discontinue nephrotoxic medications and dose adjust to creatinine clearance • Evaluate potential alternative aetiologies (recent IV contrast, medications, fluid status, UTI) • Spot urine protein/creatinine ratio	Mild (G1) (Creatinine 1.5–2x above baseline; increase of ≥ 0.3 mg/dL)	• Consider holding immunotherapy • Follow creatinine and urine protein every 3–7 days
		Moderate (G2) (Creatinine 2–3x above baseline)	• Hold immunotherapy • Follow creatinine and urine protein every 3–7 days • Nephrology consultation • Start prednisone 0.5–1 mg/kg/day if other causes are ruled out • For persistent G2 beyond 1 week, prednisone/methylprednisolone 1–2 mg/kg/day
		Severe (G3) (Creatinine > 3x baseline or > 4.0 mg/dL) Life-threatening (G4) (Creatinine > 6x baseline; dialysis indicated)	• Permanently discontinue immunotherapy • Consider inpatient care • Prednisone/methylprednisolone 1–2 mg/kg/day • Nephrology consultation • Consider renal biopsy • Consider adding one of the following if > G2 after 1 week of steroids: ✓ Azathioprine

AE	Assessment	Grading		Management
				✓ Cyclophosphamide (monthly) ✓ Cyclosporine ✓ Infliximab ✓ Mycophenolate
Ocular Adverse Event(s)				
Vision changes	Vision testing by or under the guidance of ophthalmology to include: • Visual acuity in each eye • Colour vision • Pupil size, shape, and reactivity • Red reflex • Fundoscopic examination	Uveitis	Mild (G1)	• Continue immunotherapy • Artificial tears • Refer to ophthalmology
			Anterior uveitis (G2)	• Hold immunotherapy • Urgent ophthalmology consultation • Treatment guided by ophthalmology to include ophthalmic and systemic prednisone/methylprednisolone
			Posterior or Pan-uveitis (G3) • 20/200 vision (G4)	• Permanently discontinue immunotherapy • Urgent ophthalmology consultation • Treatment guided by ophthalmology to include ophthalmic and systemic prednisone/methylprednisolone
		Episcleitis	Mild (G1)	• Continue immunotherapy • Artificial tears • Refer to ophthalmology
			20/40 vision or better (G2)	• Hold immunotherapy • Urgent ophthalmology consultation • Treatment guided by ophthalmology to include ophthalmic and systemic prednisone/methylprednisolone

AE	Assessment	Grading		Management
			• Worse than 20/40 (G3) • 20/200 vision (G4)	• Permanently discontinue immunotherapy • Urgent ophthalmology consultation • Treatment guided by ophthalmology to include ophthalmic and systemic prednisone/methylprednisolone
Nervous System Adverse Event(s)				
Myasthenia gravis	• Acetylcholine receptor (AChR) antibodies and anti-muscle-specific tyrosine kinase antibodies in blood (not needed for diagnosis) • Pulmonary function assessment with negative inspiratory force (NIF) and vital capacity (VC) • Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatine phosphokinase (CPK), aldolase for possible superimposed myositis • If respiratory insufficiency or elevated CPK, perform cardiac exam, ECG, troponin, and TTE for possible concomitant myocarditis	Moderate (G2)		• Hold immunotherapy • Pyridostigmine 30 mg TID and gradually increase to maximum of 120 mg orally four times a day as tolerated and based on symptoms. • Consider low-dose oral prednisone 20 mg daily. Increase by 5 mg every 3–5 days to a target dose of 1 mg/kg/day but not more than 100 mg daily (steroid taper based on symptom improvement)
		Severe (G3–4)		• Permanently discontinue immunotherapy • Inpatient care (may need intensive care unit [ICU]-level monitoring) • Methylprednisolone 1–2 mg/kg/day (steroid taper based on symptom improvement) • Initiate plasmapheresis or IVIG (2 g/kg) if no improvement/worsening on steroids or severe symptoms • Frequent pulmonary function assessment • Daily neurologic evaluation • Avoid medications that can worsen myasthenia

AE	Assessment	Grading	Management
	• Electromyography (EMG) with repetitive stimulation and nerve conduction study (NCS) • Neurology consultation • Consider MRI brain and/or spine depending on symptoms to rule out CNS involvement by disease		
Guillain-Barré syndrome (GBS)	• Inpatient care with access to ICU-level monitoring • Neurology consultation • MRI of spine with or without contrast (rule out compressive lesion) • Lumbar puncture • Serum antibody tests for GBS variants (GQ1b for Miller Fisher variant associated with ataxia and ophthalmoplegia) • Pulmonary function testing (negative inspiratory force [NIF]/vital capacity [VC])	Moderate (G2) or Severe (G3–4)	• Permanently discontinue immunotherapy • Inpatient care with capability of rapid transfer to ICU-level monitoring • Start IVIG (2 g/kg) or plasmapheresis in addition to pulse-dose methylprednisolone 1 gram daily for 5 days • Frequent neurologic evaluation and pulmonary function monitoring • Monitor for concurrent autonomic dysfunction • Non-opioid management of neuropathic pain
Peripheral neuropathy	• Evaluate for other causes of neuropathy such as: medication, infection, metabolic/endocrine disorders, environmental	Mild (G1)	• Consider holding immunotherapy • Monitor symptoms for a week

AE	Assessment	Grading	Management
	exposures, vascular or autoimmune disease, trauma, etc. • Consider neuraxial imaging as per neurology		
	• Evaluate for other causes of neuropathy such as: medication, infection, metabolic/endocrine disorders, environmental exposures, vascular or autoimmune disease, trauma, etc. • Neuraxial imaging as per neurology • Consider EMG/NCS • Consider neurology consultation	Moderate (G2)	• Hold immunotherapy • Initial observation or initiate prednisone 0.5–1 mg/kg orally (if progressing from mild) • If progression, initiate methylprednisolone 2–4 mg/kg/day and see Guillain-Barré Syndrome • Gabapentin, pregabalin, or duloxetine for pain
	• See Guillain-Barré Syndrome	Severe (G3–4)	• See Guillain-Barré Syndrome
Aseptic meningitis	• MRI brain with and without contrast + pituitary protocol • AM cortisol, to rule out adrenal insufficiency • Consider lumbar puncture • Consider neurology consultation		• Hold immunotherapy if mild/moderate • Permanently discontinue immunotherapy if severe • Inpatient care (G3–4) • Consider IV acyclovir until polymerase chain reaction (PCR) results obtained • Rule out bacterial and viral infection, then may closely monitor off steroids or consider prednisone 0.5–1 mg/kg/day or

AE	Assessment	Grading	Management
			methylprednisolone 1–2 mg/kg/day if moderate/severe symptoms
Encephalitis	• Neurology consultation • MRI brain with and without contrast • Lumbar puncture • EEG to evaluate for subclinical seizures • Comprehensive metabolic panel, CBC, ESR, CRP, antineutrophil cytoplasmic antibody (ANCA) (if vasculitic process suspected), thyroid panel including TPO and thyroglobulin • Autoimmune encephalopathy and paraneoplastic panel in CSF and serum		• Hold immunotherapy if mild • Permanently discontinue immunotherapy if moderate/severe • Inpatient care (G3–4) • Consider IV acyclovir until PCR results obtained • Trial of methylprednisolone 1–2 mg/kg/day • If severe or progressing symptoms or oligoclonal bands present, consider pulse steroids methylprednisolone 1 g IV daily for 3–5 days plus IVIG • If positive for autoimmune encephalopathy antibody or limited or no improvement, consider rituximab
Transverse myelitis	• Neurology consultation • MRI of spine and brain • Lumbar puncture • B-12, HIV, rapid plasma reagin (RPR), ANA, anti-Ro/La antibodies, TSH, aquaporin-4 IgG, paraneoplastic panel for anti-Hu and anti-CRMP5/CV2	Severe (G3–4)	• Permanently discontinue immunotherapy • Inpatient care • Methylprednisolone pulse dosing 1 g/day for 3–5 days • Strongly consider IVIG or plasmapheresis

AE	Assessment	Grading	Management	
	• Evaluation for urinary retention, constipation			
Cardiovascular Adverse Event(s)				
• Myocarditis • Pericarditis • Arrhythmias • Impaired ventricular function	• Immediate cardiology consultation • ECG • Telemetry monitoring • Cardiac biomarkers (creatine kinase and troponin) • Inflammatory biomarkers ✓ ESR ✓ CRP ✓ WBC count • Cardiac MRI • Evaluate for other causes: ✓ Viral titres ✓ Echocardiography ✓ Biopsy if severe symptoms	Severe (G3)	• Permanently discontinue immunotherapy • Consider methylprednisolone pulse dosing 1 g/day for 3–5 days ✓ Treat until cardiac function returns to baseline, then taper over 4–6 weeks • Inpatient care	
		Life-threatening (G4)	• Permanently discontinue immunotherapy • Consider methylprednisolone pulse dosing 1 g/day for 3–5 days ✓ Treat until cardiac function returns to baseline, then taper over 4–6 weeks • If no improvement within 24 h on steroids, consider adding anti-thymocyte globulin (ATG). May also consider adding infliximab • Inpatient care	
Musculoskeletal Adverse Event(s)				
Inflammatory arthritis	• Number of joints involved • Functional assessment • X-ray, joint ultrasound, or joint MRI	Mild	• Continue immunotherapy • NSAIDs ✓ If NSAIDs ineffective, consider low-dose prednisone 10–20 mg daily × 4 weeks; if not improving, treat as moderate • Consider intra-articular steroids in affected joint(s), depending	Monitor with serial rheumatologic examinations ± ESR, CRP every 4–6 weeks after treatment

AE	Assessment	Grading	Management
			on joint location and number involved
		Moderate	• Consider holding immunotherapy i • Prednisone 0.5 mg/kg/day × 4–6 weeks, treat as severe if no improvement • If no improvement by week 4 strongly recommend rheumatology consultation
		Severe	• Hold or permanently discontinue immunotherapy • Prednisone/methylprednisolone 1 mg/kg/day ✓ If no improvement by week 2, rheumatology consultation for consideration of additional disease modifying anti-rheumatic drugs depending on clinical phenotype of inflammatory arthritis. Options include: infliximab, methotrexate, tocilizumab, sulfasalazine, azathioprine, leflunomide, IVIG
Myalgias or Myositis	• Comprehensive metabolic panel	Mild pain	• Continue immunotherapy • Monitor serial aldolase/creatine kinase • Pain treatment as indicated

AE	Assessment	Grading	Management
	• Check creatine kinase/aldolase levels	Moderate or severe or life-threatening	• Hold immunotherapy if levels elevated • Muscle MRI and EMG • Prednisone 1–2 mg/kg/day • Consider muscle biopsy, especially in severe or refractory cases. Consider concomitant myasthenia gravis. • Monitor serial aldolase/creatine kinase until symptoms resolve or steroids discontinued • Pain treatment as indicated

Principles of Immunosuppression
• These immunosuppression recommendations are for patients receiving immune checkpoint inhibitor immunotherapy. • Close consultation with disease-specific subspecialties is encouraged. ✓ Referral to a tertiary care centre may be required for management of complex cases or multi-system irAE. • Corticosteroids are the mainstay of treatment of the majority of irAE related to immunotherapy. ✓ Early intervention with corticosteroids is a key goal in the general management of immune-related toxicity. ✓ Use of corticosteroids to treat irAE has not been shown to reduce anti-tumour efficacy. ✧ In the absence of specific indications such as prior infusion reaction and nausea, routine premedication with corticosteroids is not recommended given the potential mitigation of immunotherapeutic effectiveness in the prophylactic setting. ✓ Longer steroid tapers (> 4 weeks, sometimes 6–8 weeks or longer) may be required to prevent recurrent irAE events, particularly pneumonitis and hepatitis. ✓ See individual toxicity pages for specific recommendations on steroid dose by grade. Where immunotherapy rechallenge is indicated, see "Principles of Immunotherapy Rechallenge" (IMMUNO-C) for guidance by organ site. ✓ Prophylaxis against pneumocystis jiroveci pneumonia (PJP) can be considered in patients receiving a prednisone equivalent of 20 mg or more daily for 4 or more weeks. ✓ Prophylaxis against fungal infections (e.g., fluconazole) can be considered in patients receiving a prednisone equivalent of 20 mg or more daily for 6–8 or more weeks. ✓ Proton pump inhibitor therapy or H2 blockers can be considered for patients at higher risk of gastritis (e.g., NSAID use, anticoagulation) for the duration of corticosteroid therapy. ✓ Higher potency (e.g., Class 2 or Class 3) topical corticosteroids are preferred for short-term use for immune-related dermatitis, compared to longer term use of lower potency steroids.

- ✓ For neurologic, or Grade 3 or Grade 4 irAE, higher dose steroids (e.g., methylprednisolone or prednisone 1–2 mg/kg/day) should be given.
- ✓ If patients need to be on long-term steroids, they are at risk of developing osteoporosis. Vitamin D and calcium supplementation should be provided to prevent osteoporosis.
- • Selected irAE including hypothyroidism and other endocrine irAE may be treated with hormonal supplementation, without the need for corticosteroid therapy. See Endocrine Toxicities section.
- • Anti-TNFα agents should be avoided in patients with immune-related hepatitis. Anti-TNFα agents (e.g., infliximab) are particularly effective in the management of immune-related colitis and inflammatory arthritis.
- ✓ There is a risk for hepatitis B virus reactivation with infliximab. Test for viral hepatitis B and hepatitis C prior to TNF inhibition and monitor HBV/HCV carriers during and for several months after therapy
- ✓ There is a risk for tuberculosis (TB) activation. Test for latent/active TB prior to TNF inhibition. TB testing should not delay initiation of anti-TNFα agents for the management of irAE.
- ✧ Results of TB testing need not be finalised prior to dosing anti-TNFα agents in the acute setting.
- ✧ Interferon-gamma release assays for TB testing are preferred.
- ✓ For patients with severe irAE not responsive to steroids within 48–72 h, early (~72 h) initiation of anti-TNFα therapy (e.g., infliximab 5 mg/kg) may be warranted in consultation with the relevant medical specialist.
- ✧ A second dose of anti-TNFα therapy may be required and can be administered 2 weeks after the initial dose of infliximab.
- ✧ Anti-TNFα agents should be avoided in patients with immune-related hepatitis.
- ✧ Alpha-4 beta-7 integrin inhibitors (e.g., vedolizumab) may be considered in these cases for management of concomitant hepatitis and immune-related colitis.
- ✧ Other immunosuppressive agents may be of use in certain irAE; see individual toxicity pages.
- • Patients with pre-existing autoimmune conditions or organ transplant recipients may be candidates for immune checkpoint blockade.
- ✓ Anti-CTLA-4-based therapy has a higher incidence of exacerbating baseline autoimmune conditions relative to anti-PD-1/PD-L1-based approaches.
- ✓ Optimisation of immunosuppression for pre-existing autoimmune conditions, including close follow-up with pertinent subspecialists, is recommended.
- ✧ Goal of immunosuppressive regimen allowing for a dose of prednisone < 10 mg daily or equivalent prior to initiating cancer immunotherapy.
- ✧ Patients with solid organ transplantation may be candidates for immunotherapy, particularly if no prior evidence of graft rejection and if on maintenance immunosuppression. Graft failure while on cancer immunotherapy has been reported. Transplant organ loss may be an outcome of treatment with cancer immunotherapy and should be discussed with patient and organ transplant team.
- ✧ Patients with autoimmune neurologic conditions or life-threatening autoimmune disorders, particularly if not controlled with immunosuppressive medications or requiring high doses of immunosuppression, are unlikely to be suitable candidates for cancer immunotherapy.
- ✓ Patients with prior allogeneic stem cell transplant may be candidates for immunotherapy.
- ✧ There is an increased risk of transplant-related complications, including potentially fatal graft-versus-host disease (GVHD).
- ✧ Careful discussion with patient and stem cell transplant physicians should precede the initiation of immunotherapy.
- • Patients with a history of HIV or viral hepatitis may be candidates for immunotherapy.
- • Vaccines that are inactivated or killed preparations are permissible during a course of immunotherapy. There is less clarity regarding live vaccine use and there should be an educated discussion with the patient prior to the administration of live vaccine.

<table>
<tr><th colspan="2">Principles of Immunotherapy Rechallenge</th></tr>
<tr><td colspan="2">General Principles:

• Exercise caution when considering resumption of immunotherapy after significant irAE. Close follow-up should be performed when resuming immunotherapy to monitor for recurrent symptoms.
• If re-challenged and toxicity returns, permanently discontinue class of immunotherapy.
• Permanent discontinuation of a given class of immunotherapy is typically warranted in the setting of severe irAE induced by that class of immunotherapy and may be warranted in the setting of moderate irAE. For example, if a patient experiences Grade 3 or Grade 4 toxicity from an ipilimumab-containing regimen, consideration may be given to later therapy with a PD-1 or PD-L1 monotherapy after the resolution of earlier toxicity.
• With some exceptions, resumption of immunotherapy following Grade 2 irAE can be considered upon resolution to ≤ Grade 1.
• Consult with organ-specific specialists prior to the resumption of immunotherapy as appropriate following an immunotherapy hold due to irAE.</td></tr>
<tr><td colspan="2">Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold</td></tr>
<tr><td>Skin</td><td>• Maculopapular rash and/or pruritus: Consider resuming after symptoms have resolved to ≤ Grade 1 (i.e., once skin condition is mild/localised with only topical intervention indicated).
• Permanent discontinuation of immunotherapy in the setting of severe or life-threatening bullous disease (Grade 3 and Grade 4), including all cases of SJS and TEN.</td></tr>
<tr><td>GI</td><td>• PD-1/PD-L1 agents: After Grade 2 and Grade 3 colitis, consider resumption of immunotherapy after symptoms have resolved to ≤ Grade 1. In rare circumstances in which the patient cannot completely taper off steroids, immunotherapy may be resumed while the patient is still on ≤ 10 mg prednisone equivalent daily.</td></tr>
<tr><td>Liver</td><td>• Transaminitis without elevated bilirubin: following a Grade 2 irAE, consider resumption of immunotherapy after ALT/AST return to baseline and steroids, if used, have been tapered to ≤ 10 mg prednisone equivalent daily.
• Permanent discontinuation is warranted in the setting of severe or life-threatening (Grade 3 and Grade 4) hepatitis.</td></tr>
<tr><td>Pancreas</td><td>• Symptomatic Grade 2 pancreatitis: Consider resumption of immunotherapy if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase. Consider consultation with a pancreatic-related specialist regarding resumption.
• Permanent discontinuation is warranted for severe (Grade 3 and Grade 4) pancreatitis.</td></tr>
</table>

Endocrine	• Thyroid: No discontinuation required for hypothyroidism. For symptomatic hyperthyroidism resembling Graves-like disease, consider holding immunotherapy and resuming after workup is complete and there is evidence for improvement in symptoms and TFTs. • Primary adrenal insufficiency: After appropriate replacement endocrine therapy is instituted, immunotherapy may continue. • Hypophysitis manifested by the deficiency of TSH/ACTH and/or gonad-stimulating hormones, but without symptomatic pituitary swelling: Immunotherapy may continue while replacement endocrine therapy is regulated. • Hypophysitis accompanied by symptoms of pituitary swelling (e.g., headache, vision disturbance, and/or neurologic dysfunction): Hold immunotherapy until resolution of symptoms after steroid therapy; consider resumption of immunotherapy after symptoms are controlled on < 10 mg daily steroid dose. • T1DM with DKA: Consider resuming once DKA has been corrected and glucose level has stabilised.
	• Progressive Grade 1 pneumonitis requiring a hold: Consider resuming upon radiographic evidence of improvement. • Grade 2: Resume once pneumonitis has resolved to ≤ Grade 1. • Permanent discontinuation is warranted in the setting of severe (Grade 3 and Grade 4) pneumonitis
Kidney	• Grade 1 and Grade 2 renal irAE: Hold immunotherapy per guidelines; upon resolution to ≤ Grade 1, consider resuming concomitant with steroid if creatinine is stable. • Permanent discontinuation is warranted in the setting of severe (Grade 3 and Grade 4) proteinuria.
Eye	• Grade 2 irAE: Hold immunotherapy per guideline; consider resumption of immunotherapy in consultation with ophthalmology upon resolution to ≤ Grade 1. • Permanent discontinuation of immunotherapy is warranted in the setting of severe (Grade 3 and Grade 4) uveitis or episcleritis.
Nervous System	• Myasthenia gravis: Consider resuming immunotherapy after moderate (Grade 2) AE based on steroid responsiveness. Permanently discontinue immunotherapy after Grade 3 and Grade 4 AE. • GBS: Permanently discontinue immunotherapy for any-grade GBS. • Peripheral neuropathy: Following hold for Grade 1 and Grade 2 AE, consider resuming if symptoms resolve to ≤ Grade 1 or if a patient has well-controlled isolated painful sensory neuropathy. • Aseptic meningitis: Consider resuming following mild to moderate AE if symptoms resolve to Grade 0. • Encephalitis: Permanent discontinuation is warranted in the setting of moderate to severe encephalitis (Grade 2 to Grade 4).

	• Transverse myelitis: Discontinuation of immunotherapy following any-grade transverse myelitis.
Cardiovascular	• Grade 1 myocarditis: Consider resuming upon resolution of symptoms. • Permanent discontinuation is warranted in the setting of myocarditis (Grade 2 to Grade 4)
Musculoskeletal	• Inflammatory arthritis (moderate to severe irAE requiring hold): Resume upon stabilisation or adequate management of symptoms. • Permanent discontinuation may be warranted for severe inflammatory arthritis that significantly impairs ADLs and quality of life.

10.11 Appendix 9: Prohibited Traditional Chinese Medicines

Prohibited Traditional Chinese Medicines	
Hua Zheng Hui Sheng Tablet	Anticancer Ping Pill
Brucea Javanica Oil Soft Capsule/Brucea Javanica Oil Injection	Fu Kang Capsule
Zhe Mu Syrup	Xiao Ai Ping
Cantharidin/Cantharidin Injection/Cantharidin Capsule	Ping Xiao Capsule
Hua Chan Su	Ping Xiao Tablet
Toad Venom	Shen Dan San Jie Capsule
Kang Ai Injection	An Kang Xin Capsule
Kang Lai Te	Bo Sheng Ai Ning
Herba Sarcandrae Injection	Zedoary Turmeric Oil Glucose Injection
Ai Di Injection	Kang Li Xin Capsule
A Wei Hua Pi Cream	Ci Dan Capsule
Shenmai	Lightyellow Sophora Root
Placental Polypeptide	

Note: Traditional Chinese medicines prohibited during the trial include but not limited to the above drugs.

10.12 Appendix 10: Abbreviations

Abbreviation	Explanation
ADA	Anti-drug antibody
ADL	Activities of Daily Living
AE	Adverse events
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
APTT	Activated partial prothrombin time
ASCO	American Society of Clinical Oncology
AST	Aspartic transaminase
AUC	Area under the concentration-time curve
BUN	Blood urea nitrogen
CFDA	China Food and Drug Administration
CI	Confidence interval
CNS	central nervous system
Cmax	maximum (or peak) serum concentration
COVID-19	Coronavirus disease 2019
CR	Complete response
Cr	Creatinine
CrCl	Creatinine clearance
CRA	Clinical research associate
CSM	Clinical site manager
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	12 lead electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture system
EOT	End-of-Treatment
ESCC	Esophageal squamous cell carcinoma
ES-SCLC	Extensive stage small cell lung cancer
EQ-5D-5L	5-level EQ-5D version
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Scale
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FFPE	Formalin-fixed paraffin embedded

Abbreviation	Explanation
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good Clinical Practice
Hb	Hemoglobin
HbcAb	Hepatitis B core antibody
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HR	Hazard Ratio
HRQoL	Health-related quality of life
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICU	intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IO	Immunotherapy
INR	International normalized ratio
IRB	Institutional Review Board
IRRC	Independent Radiology Review Committee
irAEs	Immune-related adverse events
ITT	Intent-to-treatment set
IV	Intravenous
IVIG	Intravenous immunoglobulin
IWRS	Interactive web response system
IO	Immunotherapy
LFT	Liver function test
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MTD	Maximum tolerated dose
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NMPA	National Medical Products Administration
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PCP	Pneumocystis pneumonia

Abbreviation	Explanation
PD	Progressive disease
PD-L1	Programmed cell death-ligand 1
PET-CT	Positron emission tomography – computerized tomography
PD-1	Programmed cell death 1
PFS	Progression-free survival
PK	Pharmacokinetics
PKS	PK analysis set
PLT	Platelet
PPS	Per protocol set
PR	Partial response
PT	Prothrombin time
RECIST	Response Evaluation Criteria in Solid Tumors
RO	Receptor occupancy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCLC	Small cell lung cancer
SD	Stable disease
SoA	Schedule of Activities
SMP	Safety Management Plan
SOP	Standard operating procedure
T3	Triiodothyronine
T4	Thyroxine
TB	Total bilirubin
TEAE	Treatment emergent adverse event
TMB	Tumor mutation burden
TNF	Tumor necrosis factor
TPS	Tumor proportion scores
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	Ultrasound

11 References

1 Siegel R L , Miller K D , Jemal A . Cancer statistics, 2018.[J]. Ca A Cancer Journal for Clinicians, 2018, 60(5):277-300.

2 Chen Wan-qing, Sun Ke-xin, Zheng Rong-shou, et al.Report of Cancer Incidence and Mortality in Different Areas of China，2014 [J]. China cancer, 2018, 27(1): 1-14.

3 Eskandar A, Ahmed A, Daughtey M, et al. Racial and sex differences in presentation and outcomes of small cell lung cancer in the United States: 1973 to 2010[J]. Chest, 2015,147(4): e164-e165

4 Klautke G , Sauer R , Fietkau R . Combined Treatment Modality in Small Cell Lung Cancer[J]. Strahlentherapie Und Onkologie, 2008, 184(2):61-66.

5 Kurup A, Hanna NH. Treatment of small cell lung cancer[J]. Crit Rev Oncol Hematol, 2004, 52: 117-126.

6 彭红. 肺癌住院病例的流行病学特征及预后随访研究[D]. 上海: 复旦大学, 2010.

7 Puglisi M , Dolly S , Faria A , et al. Treatment options for small cell lung cancer – do we have more choice?[J]. Br J Cancer, 2010, 102(4):629-638.

8 Ishida Y , Agata Y , Shibahara K , et al. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death[J]. Embo Journal, 1992, 11(11):3887-3895.

9 Stadler S, Weina K, Gebhardt C, et al. New therapeutic options for advanced non-resectable malignant melanoma[J]. Adv Med Sci, 2015, 60(1):83-88.

10 Basso D,Fogar P,Falconi M,et al.Pancreatic tumors and immature immunosuppressive myeloid cells in blood and spleen：role of inhibitorv co-stimulatorv molecules PDLl and CTLA4.An in vivo and in vitro study[J] .PLOSONE, 2013, 8(1) :e54824.

11 Chen S, Liu H, Su N, et al. Myeloid-derived suppressor cells promote age-related increase of lung cancer growth via B7-H1[J]. Experimental Gerontology, 2015, 61:84-91.

12 Keir, M. E. Tissue expression of PD-L1 mediates peripheral T cell tolerance[J]. Journal of Experimental Medicine, 2006, 203(4):883-895.

13 Dong H, Strome S E, Salomao D R, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion[J]. Nature Medicine, 2002, 8(8):793-800.

14 Nishizumi H . Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor[J]. Immunity, 1999, 11(2):141-151.

15 Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application[J]. International Immunology, 2007, 19(7):813-824.

16 Yokosuka T, Takamatsu M, Kobayashiimanishi W, et al. Programmed cell death 1 forms negative costimulatory microclusters that directly inhibit T cell receptor signaling by recruiting phosphatase SHP2[J]. Journal of Experimental Medicine, 2012, 209(6):1201-1217.

17 Sheppard K A , Fitz L J , Lee J M , et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3ζ signalosome and downstream signaling to PKCθ[J]. Febs Letters, 2004, 574(1-3):0-41.

18 Patsoukis N, Brown J, Petkova V, et al. Selective Effects of PD-1 on Akt and Ras Pathways

Regulate Molecular Components of the Cell Cycle and Inhibit T Cell Proliferation[J]. Science Signaling, 2012, 5(230):ra46.

19 Merritt RE, Mahtabifard A, Yamada RE, et al. Cisplatin augments cytotoxic T-lymphocyte-mediated antitumor immunity in poorly immunogenic murine lung cancer[J]. The Journal of Thoracic and Cardiovascular Surgery, 2003; 126:1609-17.

20 Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. [J]. Nature Medicine, 2007, 13(9):1050-1059.

21 Remon J, Menis J, Aspeslagh S, et al. Treatment duration of checkpoint inhibitors for NSCLC. Lancet Respir Med. 2019;7 (10):835–837. doi:10.1016/S2213-2600(19)30192-4.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY		
Version	**Date**	**Notes**
Version 4.0	05 February 2021	This document Global level
Version 3.0	08 April 2020	This document
Version 2.0	27 Sep 2019	Global Level
Version 1.0	04 Mar 2019	Applicable for China only

Overall Rationale for the Amendment 3:

Protocol version 3.0 was updated to Version 4.0, based on comments from the European Medicines Agency as part of a Scientific Advice procedure, comments from the Bulgarian Drug Agency, and from the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (Poland Regulatory Agency), additional clarifications, and correction of minor inconsistencies between sections. In addition, minor corrections, including typographical/grammatical errors, have been made. Changes made during development of Version 4.0 are clarified as follows:

Section # and Name	**Description of Change(s)** (*new text is in bold and underlined, deleted text is struck-through)*	**Brief Rationale**
1.1 Synopsis 3 Objectives and Endpoints 8.3 Study Assessments 9.4.1.2 Analysis of secondary efficacy endpoints	Section 1.1 **PFS2 (assessed by the investigator based on RECIST 1.1)** Section 3 **PFS2 (assessed by the investigator based on RECIST 1.1)** Section 8.3 **Progression-free survival 2 (PFS2) is defined as time from randomization to second/subsequent objective tumor progression on next-line treatment or death from any cause.** Section 9.4.1.2 **Progression-free survival 2 (assessed by the investigator based on RECIST 1.1). PFS2 is defined as time from randomization to second/subsequent objective tumor progression on next-line treatment or death from any cause. It will be analyzed using the same method as that for PFS.**	Revision based on comments from the European Medicines Agency
1.3 Schedule of Activities (SoA)	Section 1.3 Schedule of activities table footnote #12 (initial treatment period and	Removal of myoglobin testing. It is recommended

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
8.1 Tests and Evaluations during the Study	post-PD treatment period): …myocardial **<u>function</u>** detection includes troponin-I **<u>(TnI)</u>**/ ~~or~~ troponin-T **<u>(TnT)</u>**, creatine kinase isoenzyme (CK-MB)/**<u>creatine kinase (CK), and Brain Natriuretic Peptide (BNP)/N-terminal pro-Brain Natriuretic Peptide (NT-pro BNP)</u>**~~and myoglobin~~; Section 8.1, Table 5 Myocardial **<u>function</u>**: Troponin-I **<u>(TnI)</u>**/~~or~~ **<u>Troponin-T (TnT)</u>**, Creatine kinase isoenzyme (CK-MB**<u>)/creatine kinase</u>** (CK), **<u>myoglobin Brain Natriuretic Peptide (BNP)/N-terminal pro-Brain Natriuretic Peptide (NT-pro BNP)</u>**~~, Myoglobin~~ Footnote:-**Routine blood test, blood chemistry, coagulation function, **myocardial <u>function</u>** and urinalysis	that the biomarker used for diagnosis of acute myocardial infarction is cardiac troponin due to its sensitivity and accuracy. Myoglobin remains a biomarker of secondary relevance as compared to troponin-assessments, hence it was removed.
1.3 Schedule of Activities (SoA) 5.2 Exclusion Criteria 8.1 Tests and Evaluations during the study 8.2.1 Screening Period (day -28 to day -1)	Section 1.3 Schedule of activities table: **<u>Tuberculosis screening</u>** Footnote#15 (initial treatment period) Section 5.2 Active **<u>or latent</u>** pulmonary tuberculosis. Section 8.1 and Table 5 Local laboratory tests performed at study sites include routine blood test, serum biochemistry, coagulation, myocardial enzymogram, urinalysis, thyroid function, virology, **<u>tuberculosis screening (as requested by the Bulgarian Drug Agency for Bulgarian subjects)</u>** and pregnancy test. Section 8.2.1 Local laboratory tests: routine blood test, serum biochemistry, coagulation, myocardial enzymogram, urinalysis, thyroid function,	Addition of tuberculosis testing at Screening and addition of latent tuberculosis in exclusion criteria as requested by the Bulgarian Drug Agency for Bulgarian subjects

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	pregnancy test (for females of childbearing age only)**,** ~~and~~ virology **and tuberculosis screening (as requested by the Bulgarian Drug Agency for Bulgarian subjects)**.	
2.3.2 Identified and potential risks	In the phase II study of HLX10 in patients with previously treated HCC, 1 subject received HLX10 (3 mg/kg) combined with HLX04 (5 mg/kg) once every 2 weeks experienced DLT at safety run in stage (increased total bilirubin is 39.4 ~~m~~**μ**mol/L which is >2 mg/dL and considered to be caused by hepatocellular cancer progression)	Correction of typographical error for total bilirubin unit
Sponsor Signatory	~~Xin Zhang~~**Wenying Kang** ~~Vice president~~ **Medical Director** of Global Clinical Medical Affairs	To update the Sponsor signatory information.
1.3 Schedule of Activities (SoA) 1.1 Synopsis 3 Objectives and Endpoints 8.1 Tests and Evaluations during the Study 8.2.2 Treatment Period 8.4 Safety Assessment	Section 1.3 Footnote 4# (Initial Treatment Period) ECOG performance status, serum pregnancy test, blood routine, biochemistry, coagulation, **myocardial function,** urinalysis and thyroid function (T3 or FT3, T4 or FT4, TSH) should be completed within 7 days before randomization, and the subjects should meet the corresponding inclusion/exclusion criteria for enrollment. Section 1.1 and Section 3: Safety Endpoints • Adverse events (AEs) (including serious adverse events [SAEs]), laboratory tests (routine blood test, blood chemistry, coagulation function, urinalysis, **myocardial function and** thyroid function), 12-lead electrocardiogram (12-lead ECG), vital signs, and physical examination, etc. Section 8.1 Table 5	Add “myocardial function” in laboratory tests to be consistent with Table 5.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	Routine blood test, blood chemistry, coagulation function**, myocardial function** and urinalysis must be performed at screening and within 3 days prior to drug administration every treatment cycle. Section 8.2.2 (Initial treatment visit and Post-PD treatment visit) Routine blood test, biochemistry, coagulation**, myocardial function** and urinalysis should be performed within 3 days pre-dose in each treatment cycle; for combined chemotherapy, routine blood tests should be performed on Day 8 (± 3 days) of each treatment cycle. Section 8.4 Safety assessments variables include AEs (including SAEs), laboratory tests (routine blood test, blood chemistry test, coagulation test, routine urine test, **myocardial function** and thyroid function test), 12-lead ECG, vital signs, and physical examination.	
1.3 Schedule of Activities (SoA) 8.1 Tests and Evaluations during the Study 8.2.2. Treatment Period	Section 1.3 Footnote 16# (Initial Treatment Period and Post-PD Treatment Period) Computerized tomography (CT) or magnetic resonance imaging (MRI) should be performed at screening, every 6 weeks (± 7 days) during the first 48 weeks after the start of study treatment, and every 9 weeks (± 7 days) after week 48 on sites including brain, chest, abdomen, pelvic cavity and any other sites suspected to have tumor lesions, in which brain MRI or CT (preferably MRI) and bone scans are required for all subjects at screening, and are performed in the treatment period as determined by the investigator according to clinical needs **(if baseline brain CT/MRI shows that brain metastasis is not present, the subject should have follow up brain imaging only if clinically indicated at the discretion of the investigator. If baseline brain CT/MRI has confirmed central nervous system (CNS) metastasis, continuous brain imaging test should be carried out as part of the**	Revision based on NTF clarification.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	regular RECIST evaluation assessments); examination methods at the same site should be consistent as much as possible throughout the study; if there are no contraindications, contrast agent should be used. The investigator and IRRC respectively assess the tumor images according to RECIST 1.1 (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation. If tumor assessment has been performed within 28 days prior to the first dose by the same methods and devices in the same hospital, it may serve as the baseline tumor assessment. At the EOT visit, if tumor imaging has been performed within the last 4 weeks, a re-test is not required. For subjects who discontinued for reasons other than disease progression, radiological assessments are to be continued as scheduled, until disease progression, initiation of new antineoplastic therapy, withdrawal of ICF, death, or **end of study**~~EOT~~, whichever occurs first. Section 8.1 Subjects should undergo CT or MRI (including brain, chest, abdomen, pelvic cavity and any other sites suspected of having tumor lesions) at screening (within 4 weeks pre-dose), every 6 weeks (± 7 days) during the first 48 weeks after the start of study treatment, and every 9 weeks (± 7 days) after week 48 **(if baseline brain CT/MRI shows that brain metastasis is not present, the subject should have follow up brain imaging only if clinically indicated at the discretion of the investigator. If baseline brain CT/MRI has confirmed CNS metastasis, continuous brain imaging test should be carried out as part of the regular RECIST evaluation assessments)**. Section 8.2.2	

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	Initial treatment visit and Post-PD treatment visit (Optional) **(if the baseline brain CT/MRI shows that brain metastasis is not present, the subject should have follow-up brain imaging only if clinically indicated at the discretion of the investigator. If the baseline brain CT/MRI confirms CNS metastasis, a continuous brain imaging test should be carried out as part of the regular RECIST evaluation assessments);**	
2.1 Background	**Anti-PD-1 monoclonal antibodies have been approved for melanoma, non-small cell lung cancer (NSCLC), SCLC, head and neck squamous cell cancer, urothelial carcinoma, microsatellite instability-high or mismatch repair deficient solid tumors and colorectal cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma (HCC), Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, bladder cancer, primary mediastinal large B-cell lymphoma and classical Hodgkin's lymphoma. Numerous clinical studies are ongoing with anti-PD-1 antibodies, either as monotherapy or in combination with various agents.**	Add the approved indication of anti-PD-1 antibodies in background.
2.2 Study Rationale	~~Based on the results of the HLX10 preclinical and phase I clinical trials, the currently available pharmacokinetic (PK) and anti-drug antibody (ADA) data support an average body weight dose of HLX10 of 4.5 mg/kg administered every 21 days as the recommended dose for phase III clinical studies.~~ **The available clinical data demonstrated that HLX10 is safe and tolerable in the phase I, first-in-human study in patients with advanced solid tumors, and in other clinical studies in patients with malignant solid tumors. And preliminary efficacy has been observed in some patients with advanced solid tumors in the**	Add available clinical studies information to support the study rationale.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	first-in-human phase I clinical study (HLX10-001). The safety and efficacy of HLX10 will be further evaluated in clinical studies.	
2.2 Study Rationale	Based on the results of preclinical and clinical studies, Shanghai Henlius Biotech, Inc. planned to conduct a phase III clinical study in previously untreated patients with ES-SCLC worldwide to compare the clinical efficacy **and safety** of HLX10 (recombinant anti-PD-1 humanized monoclonal antibody injection) in combination with chemotherapy (Carboplatin Etoposide).	Correcting a minor typo noted to ensure consistency and was updated in POL PA V2.1.
2.2.1 Preclinical Studies of HLX10	In the dose-finding trial (P16-106-TS), pharmacokinetic **(PK)** test (P16-106-YD), and long-term toxicity test (P16-106-CD) in *cynomolgus* monkeys; receptor occupancy (RO) at different time points was also investigated before and after intravenous injection of different doses of HLX10 to provide a basis for selection of the clinical effective dose and the initial dose.	Correcting a minor typo noted after PA V3.0 was finalized.
2.2.1 Preclinical Studies of HLX10	**Genetic Toxicology Studies** **The genotoxicity isn't required to be evaluated for monoclonal antibodies like HLX10 according to ICHS6 (R1).** ~~No genotoxicity study of HLX10 has been conducted.~~	Re-organized to clarify the genetic toxicology studies information.
2.2.1 Preclinical Studies of HLX10	Tissue cross-reactivity of HLX10 The results of tissue cross-reactivity test of HLX10 in **frozen normal** human showed that HLX10-Biotin (2.0 μg/mL and 0.5 μg/mL) specifically binds to normal human lymphocytes **from** ~~including~~ **the** lymph node~~s~~, ~~the~~ lung~~s~~, ileum, stomach, spleen, fallopian tube~~s~~, colon and thymus ~~tissues~~.	Minor update to wording for tissue cross-reactivity study
2.2.2 Clinical Study of HLX10	~~A clinical study of HLX10 had been approved by US FDA, Taiwan Food and Drug Administration (TFDA) and China NMPA.~~	The most up-to-date clinical studies are added in this protocol.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	~~Phase I clinical trial of HLX10: A prospective, open-label, dose-escalation study of HLX10 in patients with metastatic or recurrent solid tumors who had failed standard therapy. Bayesian optimal interval design (BOIN) was used to determine the maximum tolerated dose (MTD) of HLX10. The objective of this study was to evaluate the safety, PK characteristics, biomarkers, PD markers, immunogenicity and preliminary efficacy of the study drug. Eligible subjects who meet the inclusion criteria in the screening period will receive infusion of HLX10 at a dose level specified in the protocol once every 2 weeks until disease progression, or up to one year, withdrawal from study, or death, whichever occurs first. Each treatment cycle consists of two doses of study drug, once every 2 weeks. The trial is currently ongoing. The enrollment of patients into the 0.3, 1, and 3 mg/kg groups has been completed, and the safety evaluation is ongoing.~~ **To date, HLX10 has been administered to human subjects in 14 ongoing clinical studies. Clinical studies of HLX10, given as monotherapy or in combination with chemotherapy or other antibodies (anti-VEGF antibody HLX04), are being conducted in patients with advanced solid tumors, previously untreated metastatic non-squamous NSCLC, previously treated unresectable or metastatic MSI-high or mismatch repair deficiency solid tumors, previously treated advanced HCC, gastric cancer, metastatic esophageal squamous cell carcinoma (ESCC), metastatic colorectal cancer (mCRC), relapsed and/or advanced cervical cancer, and advanced head and neck cancer.** **The clinical efficacy and safety results from these studies, as well as the nonclinical toxicology and safety data, provide evidence to support continued clinical development for HLX10.**	

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
2.3.1 Potential Benefits	~~Atezolizumab (trade name Tecentriq®), a PD-L1 inhibitor developed by Roche in September 2018, has achieved landmark results in the first-line treatment of SCLC:~~ ~~IMpower 133, a randomized, controlled phase III study evaluating atezolizumab plus carboplatin-etoposide versus placebo plus carboplatin-etoposide in the treatment of untreated extensive SCLC, enrolled 403 patients and randomized at 1:1 with a median follow-up of 13.9 months. Median overall survival was 12.3 months (95% confidence interval [CI], 10.8-15.9) in the atezolizumab plus chemotherapy group and 10.3 months (95% CI, 9.3-11.3) in the placebo plus chemotherapy group (HR = 0.70, 95% CI 0.54-0.91, P = 0.007). Median progression-free survival was 5.2 months (95% CI, 4.4-5.6) in the atezolizumab plus chemotherapy group and 4.3 months (95% CI, 4.2-4.5) in the placebo plus chemotherapy group (HR = 0.77, 95% CI 0.62-0.96, P = 0.02). At the same time, in terms of safety, the safety of Atezolizumab plus chemotherapy was consistent with that in the previous reports and no new toxicity was found.~~ ~~Based on the above study results, Henlius plans to study the anti-tumor activity of HLX10 plus chemotherapy as first-line treatment of ES-SCLC. The preliminary efficacy, safety and tolerability data of PD-L1 plus chemotherapy in the IMpower 133 study supports the use of this treatment in ES-SCLC. The primary objective of this phase III study is to determine the clinical efficacy and safety of HLX10 plus chemotherapy in previously untreated ES-SCLC patients.~~ **Available clinical data for HLX10 include that collected from clinical studies of HLX10, which was given as monotherapy and/or in combination with chemotherapy or other antibody (anti-VEGF antibody HLX04), in patients with advanced solid tumors, previously untreated metastatic non-squamous NSCLC, previously treated unresectable or metastatic MSI-H or dMMR solid tumors,**	The study results of atezolizumab (IMpower 133) in this protocol will be replaced by the interim analysis results of phase I first-in-human study (HLX10-001).

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	previously treated advanced HCC, gastric cancer, metastatic ESCC, mCRC, relapsed and/or advanced cervical cancer, and advanced head and neck cancer. **The available clinical data shows that HLX10 monotherapy or combined with other therapies was safe and tolerable in patients with malignant tumors.** **Only 1 subject in the 3 mg/kg dose cohort (n=6) experienced DLT during the first cycle in the HLX10 first-in-human phase I study in patients with advanced solid tumors with four dose levels (0.3, 1, 3 and 10 mg/kg). The maximum tolerated dose (MTD) was not reached until 10 mg/kg of HLX10 was given every two weeks. Accumulation of HLX10 was observed following multiple dose administration. The 0.3 mg/kg of HLX10 was enough to saturate the PD-1 binding and induce the functional blockade. The efficacy results demonstrated anti-tumor activity of HLX10 in this first-in-human phase I study with DCR of 68.8%, ORR of 6.3%, and median PFS of 107.0 days.** **In the phase II study of HLX10 in patients with previously treated HCC, 1 subject in the dose level A (n=7) of safety run-in stage experienced DLT (increased total bilirubin is 39.4 μmol/L which is >2 mg/dL and considered to be caused by hepatocellular cancer progression).** **The study showed the anti-tumor activity of HLX10 and patients with advanced solid tumors can benefit from HLX10.**	
2.3.2 Identified and Potential Risks	~~The safety evaluation of IMpower 133 in ES-SCLC also showed that the occurrences of AEs in the atezolizumab + EC group and placebo + EC group were comparable, with the occurrences of AEs of any grade being 100% and 96.4% in the two groups, respectively; the occurrences of grade 3-4 AEs were 67.2% and 63.8% in the two groups, respectively. The occurrences of treatment-related AEs were 94.9% and~~	The safety information of atezolizumab (IMpower 133) in this protocol will be replaced by the up-to-date risk information

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	~~92.3%, respectively. The occurrences of SAEs were 37.4% and 34.7%, respectively; the occurrences of immune-related AEs were 39.9% and 24.5%, respectively. The comparisons for occurrences of most common grade 3-4 AEs: Neutropenia (22.7% and 24.5%), anemia (14.1% and 12.2%), neutrophil count decrease (14.1% and 16.8%), thrombocytopenia (10.1% and 7.7%), leukopenia (5.1% and 4.1%). The occurrences of immune-related grade 3-4 AEs in the atezolizumab + EP group were 2% for rash, 1.5% for hepatitis, 2% for infusion-related reactions, and 0.5% for pneumonia.~~ **HLX10 is currently being studied with limited safety information available. The available clinical data from the first-in-human phase I clinical study, shows that the most frequently reported study drug related adverse events were nausea, fatigue and decreased appetite, constipation, vomiting and pyrexia. The severity was mainly grade 1-2. The most frequently reported serious adverse event (SAE) that was greater or equal than grade 3 was pyrexia.** **In another phase I clinical study (HLX10HLX04-001) of the study drug combined with another antibody, no DLT was observed in the 18 subjects when the study drug was administered from 1 mg/kg to 10 mg/kg.** **In the phase II study (HLX10-008-HCC201) of HLX10 in patients with previously treated HCC, 1 subject received HLX10 (3 mg/kg) combined with HLX04 (5 mg/kg) once every 2 weeks experienced DLT at safety run in stage (increased total bilirubin is 39.4 μmol/L which is >2 mg/dL and considered to be caused by hepatocellular cancer progression).** **In the ongoing phase III study (HLX10-002-NSCLC301) of HLX10 in patients with previously untreated non-squamous non-small cell lung cancer (NSCLC), 6 subjects have received HLX10 (4.5 mg/kg) + HLX04 (15 mg/kg) + carboplatin (AUC=5) + pemetrexed**	reported in the Investigator's Brochure.

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	(500 mg/m^2) once every 3 weeks with no major safety concerns. No grade ≥4 hematologic toxicity and grade ≥3 non-hematologic toxicity-safety events and grade ≥2 pneumonia (and no recovery to grade 1 in 3 days) occurred after the treatment of the first cycles. **No serious adverse drug reactions (ADRs) were observed in the first stage of the study (safety run-in period). The most common ADRs included platelet count decreased, white blood cell count decreased, neutrophil count decreased and hypertriglyceridaemia.** **Several other phase II and III clinical studies of the study drug are ongoing, where HLX10 has been administered as monotherapy and/or in combination with chemotherapy or other antibody, in patients with advanced solid tumors, previously untreated metastatic non-squamous non-small cell lung cancer and previously treated unresectable or metastatic MSI-H (microsatellite instability-high) or dMMR (deficiency in mismatch repair) solid tumors. The available clinical data showed that the study drug given as a monotherapy or combined with other therapies was safe and tolerable in patients with malignant tumors.** **The most commonly reported side effects with probability greater than 5% include: rash, pyrexia, anemia, diarrhea, nausea, decreased appetite, platelet count decreased, white blood cell count decreased, neutrophil count decreased, nephritis, hepatic function abnormal, and hypothyroidism.** **Adverse events related to the study drug reported in these studies which are serious, fatal and life-threatening include: pyrexia, myocarditis, platelet count decreased, neutrophil count decreased, white blood cell count decreased, pneumonitis, hepatic function abnormal, colitis, pancreatitis, and renal impairment.** **More detailed information about the known and expected risks of HLX10 can be referred to in the Investigator's Brochure.**	

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2.3.3 Overall benefits: risk and ethical assessment	**Based on the current study data of HLX10, only 2 subjects experienced DLTs (1 subject received HLX10 monotherapy [3 mg/kg] once every 2 weeks, and 1 subject received HLX10 [3 mg/kg] combined with HLX04 [5 mg/kg] once every 2 weeks), the MTD was not reached yet.** ~~No dose-limiting toxicity was observed based on the current first-in-human study data for HLX10, and t~~**T**he available safety data and ~~pharmacokinetic~~**PK** data demonstrate**d** that the safety of HLX10 in patients is acceptable **and adequate** ~~enough~~ to support the implementation of this phase **III** ~~of the~~ clinical study.	Add the latest reported clinical study results.
4.3 Justification for Dose	Based on the results of the ~~HLX10~~ preclinical and **clinical** ~~phase I clinical~~ trials **of HLX10**, the currently available PK and ADA data support **HLX10 4.5 mg/kg based on mean body weight,** ~~an average body weight dose of HLX10 of 4.5 mg/kg~~ administered every 21 days as the recommended dose for phase III clinical stud**y**~~ies~~. Results of Dose Exposure Response analysis demonstrated both 4.5 mg/kg every three weeks and 3.0 mg/kg every two weeks were oversaturated doses. Given the fact that no ~~maximum tolerated dose (~~MTD~~)~~ was observed in anti-PD-1 antibodies and the European Medicines Agency~~EMA~~ and FDA approved oversaturated doses for nivolumab (nivo) and pembrolizumab (pembro) in clinical practice across multiple tumor types, Henlius believes that 4.5 mg/kg every three weeks or 3.0 mg/kg every two weeks is justified and safe.	Updates based on POL PA V2.1.
8.1 Tests and Evaluations during the Study 8.2.2 Treatment Period 8.3 Study Assessments	Section 8.1 Tumor imaging Images will be assessed by the IRRC according to RECIST v1.1 (see Appendix 2-1: Response Evaluation Criteria in Solid Tumors (RECIST 1.1)) ~~and iRECIST criteria (see~~ Appendix 2-2: iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics ~~immunotherapeutics)~~.	To clarify that IRRC will only be assessing based on RECIST 1.1 and investigator will assess based on RECIST 1.1 and iRECIST.

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	The investigator ~~and IRRC respectively~~ assesses the tumor images according to RECIST 1.1 **and iRECIST** (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation. **The IRRC assess the tumor images according to RECIST 1.1.** At the EOT visit, if tumor imaging has been performed within the last 4 weeks, a re-test is not required. **Note: For all tumor imaging timepoints, investigator must assess all the tumor images according to RECIST 1.1 and iRECIST.** Section 8.2.2 Initial treatment visit The investigator ~~and IRRC~~ should assess the tumor images according to RECIST 1.1 **and iRECIST** (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation. **The IRRC should assess the tumor images according to RECIST 1.1.** Post-PD treatment visit The investigator should assess the tumor images according to RECIST 1.1 **and iRECIST** (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation. Section 8.3	

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	Except overall survival, other efficacy endpoints are evaluated based on tumor response as per RECIST 1.1 **and iRECIST**.	
8.2.1 Screening Period (day -28 to day -1)	**Note: All reports from diagnostic procedures, which were performed before the ICF is signed and as part of the standard of care in the region and the examination methods/devices meet the study requirements might be used for the eligibility evaluation during the screening. This option restricted to those cases only, where the patient has given written confirmation that he/she consent to use his/her diagnostic reports of performed procedures before the date of ICF signature for eligibility evaluation of the actual study.**	Updates per NtF for PA V3.0.
6.2 Dosing Regimen Preparation/Handling/Storage/ Accountability	The infusion of investigational product is completed between 30 mins and 90 mins if there is not any infusion reaction. **The diluted drug solution is recommended to be used within 6 hours of preparation and has been shown to be stable for up at 24 hours. The diluted drug solution needs to be stored at approximately 2-8 °C for no longer than 24 hours and be kept from light if not used within 6 hours.**	Updates per IB 4.0 following stability testing.
1.1 Synopsis 6.6 Dose Modification	Section 1.1 In the event of intolerance to etoposide/carboplatin, the dose can be modified **twice** according to the etoposide/carboplatin prescribing information and local standard-of-care. **Once reduced, the dose cannot be increased back to 100%.** If treatment is delayed due to intolerance to chemotherapy, chemotherapy may be delayed to the next cycle of administration, with the maximum permissible interval for chemotherapy not exceeding 6 weeks. Section 6.6	Alignment of 'principles for chemotherapy modification' text between sections and removal of dose modification table for chemotherapy as in practice, the dose of carboplatin would be re-calculated before each dose.

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	Principles for chemotherapy dose modifications In the event of intolerance to etoposide/carboplatin, doses may be adjusted twice in accordance with the prescribing information of carboplatin and etoposide, **<u>the investigator's decision based on the subject's safety,</u>** and local treatment standard~~s~~ **<u>practice</u>**. Once reduced, the dose cannot be increased back to 100%. ~~**Table 1: Principles for Chemotherapy Dose Modifications Toxicity**~~ ~~**Dose Level** / **Etoposide Dosing Regimen** / **Carboplatin Dosing Regimen**~~ ~~Starting Dose / 100 mg/m^2; IV infusion on Day 1, 2 and 3 of each 3-week (21-day) cycle. / AUC = 5, up to a dose of 750 mg, IV infusion on Day 1 of each 3-week (21-day) cycle.~~ ~~First Dose Reduction / 75% of starting dose / 75% of starting dose~~ ~~Second Dose Reduction / 50% of starting dose / 50% of starting dose~~ ~~AUC=area under the concentration-time curve; IV=Intravenous~~	
5.1 Inclusion Criteria #12	≤ 1.5×ULN; In case of > 1.5 × ULN, creatinine clearance ≥ **<u>50</u>**~~60~~ mL/min	Decrease the value of creatinine clearance as per a request from the EMA
8.2.2 Treatment Period	The tumor image used to determine disease progression can be used as the new baseline image for the post-PD treatment period if 1) **<u>within</u>** 28 days prior to receiving the first dose of HLX10 or placebo therapy and 2) No study treatment between the image and first dose of HLX10 or placebo therapy, otherwise a new baseline image must be performed prior to HLX10 or placebo treatment.	Clarification that the tumor image can be used within 28 days

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8.4.7. Pregnancy	Each fertile subject shall take appropriate contraceptive measures in a period from signing ICF through at least 6 months after the final dose of the study drug~~, and in at least 6 months after the final dose of chemotherapy drug~~.	Update of information regarding contraceptive measures
6.6 Dose Modifications	Hematological toxicities Table 1 ANC < 0.5 $\times 10^9$/L and PLT ≥ 50 $\times 10^9$/L: 75% of the **planned** ~~previous~~ dose PLT < 50 $\times 10^9$/L, regardless of ANC: 75% of the **planned** ~~previous~~ dose PLT < 50 $\times 10^9$/L with Grade 2 hemorrhage, regardless of ANC: 50% of the **planned** ~~previous~~ dose ANC < 1$\times 10^9$/L with fever ≥ 38.5 °C: 75% of the **planned** ~~previous~~ dose Non-hematological toxicities Table 2 Modified carboplatin dose by % of **planned** ~~previous~~ dose[a]	To add flexibility for investigational sites to apply dose reduction based on their standard clinical practice
8.4.1.4 Death	• Any death **(**confirmed to be PD-induced **or non-PD-induced)** should be reported as an SAE **and the death should not be reported as a separate event. The SAE report needs to be submitted** ~~and reported~~ to the clinical research associate (CRA)/clinical site manager (CSM), the sponsor, or a representative of the sponsor within 24 hrs. • ~~When a death is not (or not explicitly) due to PD, the AE resulting in this death has to be deemed as an SAE and reported to the CRA/CSM, the sponsor, or a representative of the sponsor in 24 h. The primary cause of death should be provided.~~	Rewording to avoid possible misunderstanding

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8.4.2 Serious Adverse Events	2) Life-threatening (AE occurrence leads to an immediate risk of subject death, not including those AEs that may lead to death after PD~~, e.g., drug-induced hepatitis without liver failure~~)	Update as per ICH-E2A
8.4.4 Reporting of SAEs	The sponsor ~~is legally liable to inform~~ **has a legal responsibility to notify both the** local regulatory authority and other regulatory ~~bodies~~ **agencies about the** ~~of~~ safety ~~information of the study drug~~ **of a study intervention under clinical investigation**. The ~~investigator~~ **sponsor** ~~is legally obliged and ethically responsible to report promptly SAEs to relevant regulatory bodies and health authority, the ethics committee, and the study contact specifically in charge of receiving SAE reports, and make sure safety of other subjects is guaranteed~~ **will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators**. The investigator or any person-in-charge required by local authority shall abide by local regulatory regulations on SAE reporting and report SAEs to regulatory bodies, Institutional Review Board (IRB) or Independent Ethics Committee (IEC)**, as per request**.	Updated to meet cross-countries' requirement
9.5.1 Independent Data Monitoring Committee (IDMC)	The IDMC will be established to independently oversee the blinded sample size re-estimation procedure;	Correction of typographical error
9.5 Interim Analyses	An IDMC will be established for this study for ~~blinded~~ interim analysis. This study plans to carry out an interim analysis.	Correction of text as the interim analysis will not be blinded
6.3 Measures to Minimize Bias: Randomization and Blinding	The blinding will be performed by the ~~Data Management and~~ Statistical Unit during study treatment.	Deletion of Data Management, as blinding process is not created by

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		the Data Management function.
7. Discontinuation of Study Intervention and Participant Discontinuation	7 Discontinuation of Study Intervention**,** ~~and~~ Participant Discontinuation**, and Study Termination** Section 7.1.1 Reasons for Premature Discontinuation 1. Poor **subject** compliance that has affected the efficacy and safety evaluation; 2. **The occurrence of** AEs or SAEs **in the subjects, who are deemed unsuitable to** ~~that are inappropriate to~~ continue **receiving** the study **drug** treatment as judged by the investigator; 3. Evidence of **clear disease** ~~unequivocal~~ progression or worsening of the disease; 4. A delayed ~~dosing of the~~ study drug **administration** meeting the criteria **specified in the protocol**; 5. **Subject lost** ~~loss~~ to follow-up or death **during treatment**; 6. **Subject decided to** ~~W~~withdrawal ~~of~~ informed consent; **7. Subject decides to discontinue treatment;** 8. Other reasons of discontinuation as determined by the investigator in the best interest of the subject. Section 7.1.2 Management of premature discontinuations The reasons for premature discontinuations shall be documented in the eCRF **by the investigator**.	Updates for clarity of language and provide further detail for subjects discontinuing treatment

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	All subjects who discontinue the trial prematurely (except patients who withdraw informed consent) **and agree to continued follow-up of associate clinical outcome information,** shall undergo an EOT visit and be followed up for safety **and survival**. **See Section 8.2.4 for assessments during the follow-up period.** Subjects who discontinue the trial for reasons other than disease progression **and agree to continue follow-up of associated clinical outcome information** should be radiologically followed up until disease progression, withdrawal of informed consent, death or start of a new antineoplastic therapy. All AEs present at the time of discontinuation must be followed up until the outcomes of such AEs. In case of an enrolled subject's withdrawal for any reason~~s~~, no subject replacement is permitted. **7.4 Premature Termination of Study and Site Closure** **The study may be terminated prematurely for the reasons described below, and the premature termination of the study must be approved in writing by both the principal investigator and the Sponsor, and the results of the study should be reported as required by the protocol.** **1. The study is unlikely to be completed within an acceptable time frame due to difficult enrollment of subjects;** **2. The investigator doubts the safety of the drug during the study, and believes that continuing the study will bring serious risks to the subjects;**	

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	3. <u>The principal investigator and the Sponsor believe that it is necessary to terminate the study prematurely based on the number of AEs and their severity;</u> **4. <u>The expected efficacy cannot be reached, and it is not necessary to continue the clinical study;</u>** **5. <u>Withdrawal of the study by the drug regulatory authority;</u>** **6. <u>The Sponsor has the right to decide to terminate the study in a study site if the following occurs:</u>** • **<u>Serious violation of International Conference on Harmonization Good Clinical Practice (ICH-GCP) by the study site</u>** • **<u>Multiple serious protocol violations by the study site</u>** **<u>After termination of the study, all study-related records should be retained for reference.</u>**	
Section 5.2 Exclusion criteria Section 7.2 Participant Discontinuation/Withdrawal from the Study	Section 5.2 16. Treatment with live vaccines **<u>and all COVID-19 vaccines (fully administered to the required number of doses)</u>** within 28 days prior to study drug administration; inactivated viral vaccines for seasonal influenza are allowed. 18. Any active infection requiring systemic anti-infective therapy within 14 days prior to study drug administration **<u>or subjects with a positive RT-PCR test for SARS-CoV-2 infection at randomization. Subjects with a history of COVID-19 infection must have a negative RT-PCR test prior to the first dose of the study drug.</u>** Section 7.2 **<u>If a subject develops fever or symptoms suspected of being a result of COVID-19 during the study, they will be instructed to follow-up</u>**	Addition of information relating to subjects with or a history of COVID-19 infection

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	with their regular healthcare provider or follow the instructions for suspected COVID-19 cases per their local health authority. A subject will discontinue treatment based on discussion with the Sponsor and Medical Monitor under the following circumstances: any suspected or confirmed COVID-19 case will be immediately discontinued from study treatment for up to 12 weeks after the last study drug administration; subjects who recover from the infection within 12 weeks from the last study drug administration, can continue treatment following Sponsor's confirmation.	

Overall Rationale for the Amendment 2:

Protocol Version 2.0 was updated to Version 3.0 based on the comments from the European Medicines Agency and the United States Food and Drug Administration as part of Scientific Advice procedures.

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1.1 Synopsis 3 Objective and Endpoint Primary Efficacy Endpoint	• ~~Progression-free survival (PFS) (assessed by the independent radiology review committee [IRRC] based on Response Evaluation Criteria in Solid Tumors [RECIST] 1.1)~~ • **Overall survival (OS)**	OS is the recommended primary endpoint as 2-year survival for ES-SCLC is less than 5% and there is a limited activity in second-line therapies.
1.1 Synopsis 3 Objective and Endpoint Secondary Efficacy Endpoint	• ~~Overall survival (OS)~~ • **Progression-free survival (PFS) (assessed by the independent radiology review committee [IRRC] based on Response Evaluation Criteria in Solid Tumors [RECIST] 1.1)**	Change PFS to a secondary endpoint

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1.1 Synopsis 4.1 Overall Design	**Initial t**~~T~~reatment should be discontinued when they have evidence of disease progression as assessed by RECIST ~~v~~1.1. ~~However, considering the limited availability and efficacy or greater toxicity of treatment options after withdrawal, and for better adaptation to standard clinical practice,~~ **If a subject has 1st disease progression and is clinically stable, and tends to receive 2nd line chemotherapy treatment subsequently (the selection of 2nd line chemotherapy may refer to the NCCN guidelines or the ESMO guidelines), it is at the discretion of the investigator to continue treating the subject with blinded HLX10 or placebo assignment per protocol in addition to the 2nd line chemotherapy, until the 2nd disease progression ~~lost clinical benefit~~, intolerable toxicity, death, withdrawal of consent, or lost to follow-up. Subjects who permanently discontinue initial treatment due to an adverse event, withdrawal of consent, or for any reason other than disease progression, will not be eligible for the post-PD treatment.** ~~the s~~**Subjects who meet**~~s all~~ **the following conditions may continue the treatment** ~~and~~ **after appropriate discussion with the subject and obtaining the supplementary informed consent.** **1. Subjects who had received HLX10 or placebo in combination with chemotherapy, who may benefit from continuing HLX10/placebo treatment despite progression, will be able to receive HLX10 or placebo therapy in the post-PD treatment.** ~~1. With no clinical signs and symptoms (including worsening of laboratory findings) indicating a significant disease progression.~~ **2. Subjects eligible for continued treatment in the post-PD treatment period, as judged by the investigator.** ~~2. A stable Eastern Cooperative Oncology Group (ECOG) performance status score.~~	In combination with second-line chemotherapy in the post-PD treatment period, subjects are prevented from being exposed to placebo alone.

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	<u>3. The subject should sign the supplementary informed consent form to receive investigational product with 2nd line chemotherapy.</u> **<u>4.The subject is clinically stable, defined as:</u>** **<u>a) With no clinical signs and/or symptoms (including worsening of laboratory findings) that might indicate disease progression.</u>** **<u>b) A stable Eastern Cooperative Oncology Group (ECOG) performance status score.</u>** **<u>c) No rapid disease progression or tumor progression requiring urgent alternative medical intervention at critical anatomical sites (e.g., spinal cord compression).</u>** ~~3. No rapid disease progression or tumor progression requiring urgent alternative medical intervention at critical anatomical sites (e.g., spinal cord compression).~~ ~~4. The major organ function meets the inclusion and exclusion criteria of this study.~~ ~~5. The subject should sign the supplementary informed consent form to continue treatment.~~ ~~The primary objective of this study is to compare the PFSs of HLX10 in combination with chemotherapy versus placebo in combination with chemotherapy, as assessed by an Independent Radiology Review Committee (IRRC) using RECIST v1.1.~~	
1.1 Synopsis Treatment Groups and Duration: 8.2.2 Treatment Period	This study is divided into three periods: Screening period (28 days), treatment period **<u>(initial treatment and post-PD treatment [Optional]</u>**, until **<u>disease progression</u>** ~~loss of clinical benefit,~~ death, intolerable toxicity, withdrawal of informed consent, or occurrence of other reasons specified in the protocol, whichever occurs first), and Follow-up period (including safety follow-up and survival follow-up).	Adjustment of treatment periods because of the addition of post-PD treatment.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
1.1 Synopsis Other study drugs: combined chemotherapy 4.1 Overall Design 6.2 Dosing Regimen Preparation/Handling/Storage/Accountability 6.6 Dose Modification	Carboplatin: Area under the concentration-time curve (AUC) = 5, IV infusion, on Day 1 of each cycle up to a dose of ~~800~~**750** mg. **On Day 1, etoposide shall be administered following infusion of carboplatin.**	To adjust the maximum dosage of carboplatin according to the NCCN Chemotherapy Order Templates about Maximum Carboplatin Dose Calculation. To clarify the order of drug administration.
1.2 Schema	Screening period: **The maximum screening period is 28 days**. ~~At least 28 days.~~ Treatment period: **Including initial treatment and post-PD treatment (optional)** **After finishing the initial treatment period, patients in both arms who had 1st disease progression per RECIST 1.1 and might benefit from their assigned treatment in addition to 2nd line chemotherapy, may be eligible to continue to receive their assigned treatment in the post-PD treatment period (Optional) until the 2nd disease progression, intolerable toxicity, death, withdrawal of consent, or lost to follow-up.** Safety follow-up period: 90 days after the last **study drug administration** ~~dose~~. Safety visit is required at the site 30 days (±7 days) after the last **study drug administration** ~~dose~~, and telephone follow-up is required 90 days (±7 days) after the last **study drug administration** ~~dose~~. Survival follow-up period: Every 12 weeks ± 7 days	To keep the study periods consistent throughout the protocol.
1.3 Schedule of Activities (SoA)	~~**Study Procedures**~~ **Initial Treatment Period and Post-PD Treatment Period (Optional)**	To keep the study periods consistent throughout the protocol.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
1.3 Schedule of Activities (SoA) Initial Treatment Period footnote #7	~~Re-assessments~~ **Quality of life assessment could be performed either on Day -7 to Day -1 of the screening period or prior to dosing in Cycle 1** ~~are not required for subjects who had a quality of life assessment on Day -7 to Day -1 of the screening period.~~	To clarify the acceptable time window for performing quality of life assessment during the screening period.
1.3 Schedule of Activities (SoA) Initial Treatment Period footnote #8	**Adding footnote #8: Re-assessments prior to dosing in Cycle 1 are not required for subjects who had 12-lead ECG and ECOG scores assessment on Day -7 to Day -1 of the screening period**	To clarify the acceptable time window for performing 12-lead ECG and ECOG scores assessment during the screening period.
1.3 Schedule of Activities (SoA) Initial Treatment Period footnote #9 8.1 Tests and Evaluations during the Study	~~If the change in the subject's body weight from baseline during the study is ≤10%, dose adjustment of investigational product study drug will not be required, and if the weight change is >10%, the dose of study drug must be recalculated.~~ **If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose of investigational product, the dose of investigational product must be recalculated. All doses should be rounded to the nearest milligram.**	To substitute "study drug" with "investigational product" as investigational product stands for HLX 10/placebo only and does not include chemotherapy drugs. Language has been edited to make the dose modifications of investigational product clearer.
1.3 Schedule of Activities (SoA) Initial Treatment Period footnote #12 8.1 Tests and Evaluations during the Study Laboratory Tests	12.**serum** biochemistry items include blood urea/urea nitrogen, creatinine, sodium, potassium, magnesium, chloride, ~~carbon dioxide binding capacity or bicarbonate or total carbon dioxide~~, calcium, phosphorus, blood glucose, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase, total cholesterol, total protein, albumin; **coagulation test consist of prothrombin time (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR); myocardial enzymogram detection includes troponin-I, creatine kinase isoenzyme (CK-MB) and myoglobin**;	To delete "carbon dioxide binding capacity or bicarbonate or total carbon dioxide" from the serum biochemistry test as these items are not required but can be performed if considered standard of care in the region.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	urinalysis items include specific gravity, urine leukocytes, pH, urine glucose, urine protein, ketone body and ~~blood cells~~**urine occult blood, microscopic examination of white blood cells and red blood cells should be collected if urine leukocytes and urine occult blood are out of normal range.** Can be performed within 3 days before dosing in each cycle; for aforementioned laboratory tests scheduled on the same day as study treatment, the study treatment can be arranged only after the test results are obtained. **For laboratory tests from the screening period completed on Day -7 ~ Day -1, it is not necessary to repeat the test again before the first administration (C1D1).** For combined chemotherapy, routine blood tests should be performed on Day 8 (± 3 days) of each treatment cycle to closely monitor bone marrow suppression.	To include myocardial enzymogram detection to address safety concern. Language has been added to clarify the urinalysis items. To clarify time window of local lab test at screening period.
1.3 Schedule of Activities (SoA) Initial Treatment Period footnote #14 8.1 Tests and Evaluations during the Study Laboratory Tests	**Patients with HBsAg (+) and/or HBcAb (+)** ~~HBsAg positive subjects~~ should be further tested for hepatitis B virus (HBV) DNA titer; and HCV antibody positive subjects should be further tested for HCV RNA.	Language has been edited to clarify the HBV testing requirements.
1.1 Synopsis 9.2 Sample Size Determination 9.5 Interim Analyses	Number of Participants: Approximately ~~489~~**567** (~~326~~ **378** for HLX10 and ~~163~~**189** for placebo). Corresponding wording and recalculation were applied to section 9.2 and 9.5	Sample size was recalculated due to change of primary endpoint to OS.
2.2.2 Clinical Study of HLX10	**Phase I clinical trial of HLX10: A prospective, open-label, dose-escalation study of HLX10 in patients with metastatic or recurrent solid tumors who had failed standard therapy. Bayesian optimal interval design (BOIN) was used to determine the maximum tolerated dose (MTD) of HLX10. The objective of this study was to evaluate the safety, PK characteristics, biomarkers, PD markers,**	To make the description of phase I study clearer.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	<u>immunogenicity and preliminary efficacy of the study drug. Eligible subjects who meet the inclusion criteria in the screening period will receive infusion of HLX10 at a dose level specified in the protocol once every 2 weeks until disease progression, or up to one year, withdrawal from study, or death, whichever occurs first. Each treatment cycle consists of two doses of study drug, once every 2 weeks. The trial is currently ongoing. The enrollment of patients into the 0.3, 1, and 3 mg/kg groups has been completed, and the safety evaluation is ongoing.</u> ~~for a dose escalation phase I clinical trial. There are four dose groups (0.3, 1, 3 and 10 mg/kg, once two weeks) in the trial, with a maximum enrollment of about 30 subjects. At present, three patients in the fourth dose group have completed the enrollment, and no dose-limiting toxicity was observed in all dose groups during the dose-limiting toxicity observation period.~~	
4.1 Overall Design	The primary endpoint of this study is to compare the **OS** ~~PFSs~~ of HLX10 in combination with chemotherapy versus placebo in combination with chemotherapy~~, as assessed by an IRRC using RECIST v1.1 as evaluation criteria~~.	Change OS to primary efficacy endpoint.
4.1 Overall Design Figure 1: Schematic of study treatment	**<u>1st</u>** Disease Progression ~~The subject should re-consent and meet the following conditions:~~ **<u>The subject (tending to receive 2nd line chemotherapy treatment subsequently) should re-consent and meet the following conditions: (1) Subjects who had received HLX10 or placebo in combination with chemotherapy, who may benefit from continuing HLX10/placebo treatment despite progression, will be able to receive HLX10 or placebo therapy in the post-PD treatment period</u>** ~~With no clinical signs and symptoms (including worsening of laboratory findings) indicating a significant disease progression.~~	To keep the study design consistent throughout the document.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	(2) Subjects eligible for continued treatment in the post-PD treatment period, as judged by the investigator. ~~A stable ECOG performance status score.~~ **(3) The subject should sign the supplementary informed consent form to receive investigational product with 2nd line chemotherapy.** **(4) The subject is clinically stable.** ~~No rapid disease progression or tumor progression requiring urgent alternative medical intervention at critical anatomical sites (e.g., spinal cord compression).~~ ~~(4) The major organ function meets the inclusion and exclusion criteria of this study.~~ ~~(5) The subject should sign an informed consent form again.~~ ~~Continue the treatment until persistent disease progression, worsening of symptoms due to disease progression, or intolerant toxicities~~ **Continue the treatment until the 2nd disease progression, intolerant toxicities, death, withdrawal of consent, or lost to follow-up.** ~~Continue the treatment until persistent disease progression, worsening of symptoms due to disease progression, or intolerant toxicities~~ *** Follow-Up Period includes safety follow-up and survival follow-up. Patients who are not eligible for post-PD treatment will be followed up for safety and survival status.**	
4.2 Scientific Rationale for Study Design Rationale for Post-PD Treatment	**Patients with ES-SCLC experience rapid tumor growth, fast clinical deterioration, and have an overall poor prognosis. First-line therapy with a platinum agent and etoposide has consistently demonstrated high response rates and significant clinical benefit. However, considering the limited availability and efficacy or greater toxicity of treatment options after withdrawal, and for better adaptation to standard clinical practice, subjects may be considered for subsequent treatment assignment blinded beyond radiographic disease progression per RECIST 1.1, at the discretion of the**	To clarity the rationale for post-PD treatment.

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	investigator, after appropriate discussion with the patient and obtaining informed consent. **In addition, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because disease progression (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Related research shows that shorter treatment increases the risk of relapse or progression, and there are potential benefits to patients receiving longer IO (Immunotherapy) treatment[21]. Because of the potential for pseudoprogression/tumor-immune infiltration, this study will allow patients to remain on treatment after apparent radiographic disease progression per RECIST 1.1, provided all criteria meet post-PD treatment conditions.**	
4.4 End of Study Definition	**"**The end of the study, defined as the final analysis of ~~PFS~~ **OS,** will be performed when a target number of ~~PFS~~ **OS** events (approximately ~~336~~**342**) are observed..."	To redefine End of Study due to change of primary endpoint
5.1 Inclusion Criteria #2	Male or female **aged ≥ 18** ~~between 18 to 75 (inclusive)~~ years at the time of signing the ICF.	Remove upper age limit as patients older than 75 years represent a substantial proportion of patients with ES-SCLC.
5.1 Inclusion Criteria #6	Note: Measurable lesions are not from previously irradiated sites. If the lesion at the previously irradiated site is the only selectable target lesion, **a radiological assessment showing significant progression of the irradiated lesion should be provided by the investigator.** ~~anteroposterior images showing significant progression of the lesion should be provided by the investigator.~~	Wording re-edit.

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5.1 Inclusion Criteria #12	≤ 1.5×ULN; In case of > 1.5 × ULN, creatinine clearance ≥ **60**~~50~~ mL/min	Increase the value of creatinine clearance to take into account the renal toxicity of carboplatin.
5.1 Inclusion Criteria #13	Agree to use birth control methods with an annual failure rate of <1% or maintain abstinence (avoid heterosexual intercourse) (from the signing of informed consent form (ICF) to at least **6 months** ~~120 days~~ after the final dose of study drug ~~or at least 150 days after the final dose of chemotherapy drug~~) (birth control methods with an annual failure rate of <1% include bilateral tubal ligation, male sterilization, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine contraceptive devices and copper containing intrauterine contraceptive devices or condoms)	Extending of time limits of using birth control methods or maintain abstinence after the final dose of study drug
5.1 Inclusion Criteria #14	Male patients must: agree to abstinence (avoid heterosexual intercourse) or take contraception measures as follows: male patients with a pregnant partner or a partner with of childbearing potential must remain abstinent or use a condom to prevent embryonic exposure during **study treatment** ~~chemotherapy treatment (carboplatin or etoposide)~~ and for at least ~~150 days~~**6 months** after the last dose of **study drug** ~~chemotherapy~~. Periodic abstinence (e.g., contraceptive methods based on calendar day, ovulation, basal body temperature or post-ovulation) and external ejaculation are ineligible methods of contraception.	Extending of time limits of abstinence or use a condom to prevent embryonic exposure after the last dose of study drug.
6.2 Dosing Regimen Preparation/Handling/Storage/Accountability	Other study drugs: chemotherapy • Etoposide: 100 mg/m^2, IV infusion, on Days 1, 2, and 3 of each cycle. **On Day 1, etoposide shall be administered following infusion of carboplatin.**	To clarify the order of adminstration of study drugs
6.5 Concomitant Therapy	**6.5.3 Subsequent Anti-Cancer Therapy Status**	Adding subsequent anti-cancer therapy status, to

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	The investigator or his/her qualified designee will review all new anti-cancer therapy initiated after the discontinuation of trial treatment. If the subject continues the post-PD treatment, he/she must choose to receive 2nd line chemotherapy. The preferred 2nd line chemotherapy was determined by the investigators following the NCCN /or ESMO guidelines and communicated as such to the subjects who chose to continue the Post-PD treatment. Any other anti-PD1 and anti-PD-L1 therapy are not allowed.	clarify the concomitant therapy in post-PD treatment
6.6 Dose modification	In the event of intolerance to etoposide/carboplatin, doses may be adjusted twice in accordance with the prescribing information of carboplatin and etoposide and local treatment standards. **Once reduced, the dose cannot be increased back to 100%.** Make adjustment in" Non-hematological toxicities" in both text and table for recommended carboplatin dose modification	To make adjustment to recommended dose modification.
7.1.2 Management of premature discontinuations	All subjects who discontinue the trial prematurely **(except patients who withdraw informed consent)** shall undergo an EOT visit and be followed up for safety.	To exclude subjects who withdraw their informed consent from the EOT visit and safety follow-up.
8.2.4 Follow-Up period	During the survival follow-up period, subjects ~~without PD and not receiving any other anti-tumor therapy~~ should ~~return to the hospital according to the established schedule for radiologic assessment~~ **should be followed up** until ~~PD, initiation of a new anti-tumor therapy,~~ ICF withdrawal, death, **the patient is lost to follow-up, study termination by the sponsor,** or study completion, whichever occurs first~~.; while subjects experiencing PD or undergoing any other anti-tumor therapy just need to be followed up for survival status by telephone call once every 12 weeks (±7 days).~~	To update the condition of survival follow up

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
8.4 Safety Assessment	The structure and wording were re-edited, changes are listed below： 1. Any death confirmed to be PD-induced should be reported **as an SAE and reported to the clinical research associate (CRA)/clinical site manager (CSM), the sponsor, or a representative of the sponsor within 24 hrs.** ~~to the sponsor at the next monitoring visit. It should be documented but not reported as an SAE.~~ **2. Insert a section "8.4.2. 1 Drug-induced liver injury, (DILI)"** 3. **8.4.3.** Documentation of AEs. All AEs occurring in a period from signing ICF **(either main or supplementary)** through 90 days after the final administration of the study drug should be documented in corresponding AE pages in EDC. **If a subject starts a new antineoplastic therapy during the AE collection period, only information on AEs related to study treatment are documented after the new antineoplastic therapy.** The investigator shall provide all detailed information required to be completed, including date of onset, severity, action, outcome, and causality to the study drug. When collecting AE data, one has better recording diagnosis information (if possible), rather than recording a number of signs and symptoms. However, if a diagnosis is known but the patient still has other symptoms or signs not contributing to such diagnosis, then each symptom or sign should be documented separately. 4. Add AESI as follows: **AESIs are events of scientific and medical concern related to use of the investigate drug that may need to be closely monitored and communicated to sponsors by investigators. AESI can be a serious or non-serious event. The AESI expedited**	To rearrange this section according to the updated Pharmacovigilance rules.

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	report enables continuous monitoring of these events in order to describe and understand their association with the drug used in the study. **In this study, AESI include infusion reaction (infusion-related adverse reactions, IRR) and immune-related adverse events (irAE).** 5. Each fertile subject shall take appropriate contraceptive measures in a period from signing ICF through at least~~120 days~~ **6 months** after the final dose of the study drug and in at least ~~150 days~~ **6 months** after the final dose of chemotherapy drug. 6. The investigator will evaluate whether causality between the study drug and the AE is "~~definitely~~ related", "possibly related", "unlikely related", "~~definitely~~ unrelated", or "~~not evaluable~~ unknown". **AEs other than "unlikely related" and "not related" are recorded as adverse reactions.** ~~Any AE without given causality to the study drug will be deemed as "possibly related" to the study drug.~~ 7. **All AEs and SAEs that occur in each subject throughout the study should be actively followed up. Even if such events persist after discontinuation or study termination, the investigator should follow them up until all events meet any of the following criteria:** ~~All AEs occurring in a period from signing ICF through 90 days after the final dose of the study drug should be followed up until any of the following circumstances occurs:~~	
9.4.1 Efficacy Analyses	Analyses of the primary efficacy endpoint **and the secondary efficacy endpoints** will be performed for both the ITT and PPS, **mainly on the ITT**. ~~analyses of the secondary and exploratory efficacy endpoints will be performed for the ITT only.~~	To correct population for analyses due to changing of endpoints.
9.4.1.1 Analysis of primary efficacy endpoint	9.4.1.1 Analysis of primary efficacy endpoint **Overall survival (OS): Defined as a period from randomization through death regardless of causality. Data of patients without a**	To keep consistency in the document text after changing of endpoints.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
9.4.1.2 Analysis of secondary efficacy endpoints	**death record will be censored on the last known survival date.** ~~Progression free survival (assessed by the IRRC as per RECIST v1.1): PFS is defined as a period from randomization initiation to the first documentation of PD or death regardless of causality (whichever occurs first). Data of subjects with neither PD nor death will be censored on the day of the final valid tumor evaluation. Data of surviving subjects not undergoing any tumor assessment during the study will be censored on the day of randomization. Data of subjects who have no PD reported and initiate any antitumor therapy not specified in the protocol will be censored on the day of the last evaluable tumor assessment prior to the initiation of subsequent antitumor treatment.~~ The between-group comparison of **OS** ~~PFS~~ is performed by a stratified log-rank test with the following stratification factors: PD-L1 expression level (negative: TPS <1%, positive: TPS ≥1%, or not evaluable/not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years); a stratified COX proportional risk model will be used to estimate HR and its 95% CI; the Kaplan-Meier method will be used to estimate the median, and the Kaplan–Meier curve will be plotted. 9.4.1.2 Analysis of secondary efficacy endpoints **Progression free survival (assessed by the IRRC as per RECIST 1.1): PFS is defined as a period from randomization initiation to the first documentation of PD or death regardless of causality (whichever occurs first). Censor rules will be defined in SAP.** ~~Overall survival (OS): Defined as a period from randomization through death regardless of causality. Data of patients without death record will be censored on the last known survival date. Data of patients not providing any follow-up information will be censored on the randomization day.~~ The **PFS**~~OS~~ will be analyzed using the same method as that for primary efficacy endpoints.	

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9.4.1.3 Subgroup analyses	Add the new section as 9.4.1.3 “Subgroup analyses”	To assess the consistency of the study PFS and OS, results in subgroups will be examined.
9.5 Interim Analyses	Add the stopping boundary for OS interim and final analyses	To add description per ICH-E9
10.10 Appendix 8	Replaced Appendix 8 with NCCN Guidelines®: Management of Immunotherapy-Related Toxicities (2019 V2)	To update the guidelines
Throughout the protocol	Some editorial changes were made.	To keep the consistency throughout protocol.

Overall Rationale for the Amendment 1:

The structure of protocol Version 2.0 was updated and rearranged based on Version 1.0 in accordance with ICH guidance. Additional changes made during development of Version 2.0 are clarified as follows.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
Title page	A Randomized, Double-Blind, Multicenter, Phase III Study to ~~Evaluate~~ **Compare Clinical Efficacy and Safety of** HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin-Etoposide) in Previously Untreated Patients with Extensive Stage Small Cell Lung Cancer (ES-SCLC) A short title was added.	To include the objective in the title for clarifying the purpose and objective of the study.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
Title Page, Regulatory Agency Identifying Number(s)	**NMPA Approval Document Number: 2018L02201, EudraCT Number: 2019-003063-21**	To add the NMPA approval document Number and EudraCT Number for this protocol.
Investigator Agreement Page	Updated the Agreement pages, one page for Principal Investigator, the other page for Global Coordinating Investigator.	To provide agreement pages for Principal Investigator and the Global Coordinating Investigator.
1. Protocol Summary	Inserted a header of section 1: **protocol summary**	To give an overview of the protocol.
1.3 Schedule of Activities (SoA) footnote #11 8.1 Tests and Evaluations during the Study Laboratory Tests	total cholesterol, total protein, albumin; urinalysis items include specific gravity, **urine leukocytes**, pH, urine glucose, urine protein, ketone body and blood cells.	To include urine leukocytes for urinalysis to monitor the subject's immune response.
1.1 Synopsis 3 Secondary Efficacy Objective	Progression-free survival (PFS) assessed by the investigator based on RECIST v1.1 and ~~modified RECIST criteria~~ **a modified RECIST 1.1 for immune-based therapeutics (termed iRECIST)**.	To add consensus guideline (iRECIST) developed for the use in cancer immunotherapy trials for the evaluation of PFS.
9.4.1.2 Analysis of Secondary Efficacy Endpoints	PFS assessed by the investigator as per RECIST v1.1 **and iRECIST**: Its statistical method is the same as that for primary efficacy endpoints.	
10.4 Appendix 2-2	"Modified Response Evaluation Criteria in Solid Tumors" was replaced with "iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics".	
1.1 Synopsis 3 Objectives and Endpoints	~~Exploratory~~ ~~• Exploratory population pharmacokinetic (PopPK) analysis~~	To delete the secondary objective of "Exploratory".

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
1.1 Synopsis 1.2 Shema 4.1 Overall Design 6.3 Measures to Minimize Bias: Randomization and Blinding 9.4.1.1 Analysis of primary efficacy endpoint	Randomization are stratified by PD-L1 expression level (negative**: tumor proportion scores [TPS] <1%**, positive**: TPS ≥1%**, **or not evaluable/**not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years)	To define the limits for PD-L1 expression levels specifically.
1.3 SoA footnote #8	The height measurement is performed only at screening; vital signs include body temperature, pulse, respiratory rate, and blood pressure. Body weight ~~is measured before each dose, and no dose adjustment of the study drug is required if the subject's body weight differs ≤ 10% from the reference value of the current dose during the study, otherwise the dose should be recalculated. This new body weight will serve as the baseline value for subsequent body weight measurements.~~ **Body weight will be measured prior to drug administration at each treatment cycle. If the change in the subject's body weight from baseline during the study is ≤10%, dose adjustment of study drug will not be required, and if the weight change is >10%, the dose of study drug must be recalculated.**	To clarify the timing of bodyweight measurement to allow an adjustment of the administration dose.
1.3 SoA footnote #16	**Patients must provide tumor tissues that meet the requirements for the determination of PD-L1 expression levels. It is recommended to provide formalin-fixed tumor tissue samples, paraffin-embedded tumor specimens (preferred), formalin-fixed paraffin embedded (FFPE), tumor specimens or newly prepared unstained serial tissue sections (preferably adhesive slides) within 6 months prior to the first dose of study medication. A relevant pathology report must also be provided for the above specimens.** ~~To the extent possible, formalin-fixed paraffin-embedded (FFPE) tumor samples (paraffin~~	To clarify the tumor tissue assessment procedure and purpose.

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	~~blocks or unstained sections) collected at or after the diagnosis of ES-SCLC and within 6 months prior to the start of study medication or pathological reports of such specimens should be provided. In case of no archived tumor tissue samples available, it is recommended to conduct a fresh tumor lesion biopsy at screening to obtain the corresponding tumor sample (the number of specimens required is based on the biopsy result). Tumor tissue sections will be used for immunohistochemical analysis to evaluate the expression level of PD-L1 in tumor cells and tumor-infiltrating immune cells and other purposes.~~ Freshly collected specimens, radical resections, core needle biopsy, excisions, incisions, punch or clamp biopsies are acceptable **(newly obtained tissues are preferred).** Fine-needle aspirations (i.e., samples that lack a complete tissue structure and provide only cell suspension and/or cell smear), brush biopsies, and cell pellet samples from pleural or peritoneal effusions are unacceptable. For detailed requirements for tissue samples, see the laboratory manual.	
3 Objectives and Endpoints	~~Primary endpoint~~ **Primary Efficacy Endpoint** ~~Secondary endpoint~~ **Secondary Efficacy Endpoint** ~~• Incidence rates of AEs and SAEs~~ ~~• Pharmacokinetics (PK): serum HLX10 concentration~~ ~~• Immunogenicity evaluation: positive anti-drug antibody (ADA) rate~~ ~~• Relationship between PD-L1 expression level, MSI, TMB in tumor tissues and efficacy~~ ~~• Quality of life assessment~~ **Safety Endpoints** **• Adverse events (AEs) (including serious adverse events [SAEs]), laboratory tests (routine blood test, blood chemistry, coagulation function, urinalysis, thyroid function), 12-lead**	Endpoints classification were re-organized for better readability and to ensure the clarification of the endpoints.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	electrocardiogram (12 lead ECG), vital signs, and physical examination, etc. **PK Endpoint** **• Concentration of HLX10 in serum** **Immunogenicity Endpoint** **• HLX10 anti-drug antibody (ADA) positive rate** **Biomarker Endpoint** **• Relationship between PD-L1 expression, microsatellite instability (MSI), tumor mutation burden (TMB) in tumor tissue and efficacy.** **Quality of life assessment**	
4.Study Design	Inserted section 4.4 **End of study definition**, and description started from **"The end of the study is defined as the final analysis of PFS will be performed when a target number of PFS events (approximately 336)…etc."**	To clarify the definition of the end of the study.
5.1 Inclusion Criteria # 2	2. **Male or female between** 18 to 75 (inclusive) years at the time of signing the ICF.	To clarify the gender requirement of the subjects.
5.1 Inclusion Criteria # 7	Patients must provide tumor tissues that meet the requirements for the determination of PD-L1 expression levels. Subjects are assessed for an evaluable PD-L1 expression category (negative: **TPS <1%,** positive: **TPS ≥1%,** or **not evaluable/**not available) by the central laboratory for randomization.	To define the limits for PD-L1 expression levels specifically.
5. study population	1. Inserted section 5.3 **Lifestyle Consideration** and description of "**No restrictions are required**."	1. To clarify the concerns to the subject's lifestyle and to

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	2. Inserted section 5.4 **Screen failures** and description started from "**Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure…etc.**"	follow the common protocol template structure. 2. To clarify the definition of screen failures and the information required.
6. Study Intervention	Inserted the new header of Section 6 **Study Intervention** and description started from "**Study drug is defined as any investigational interventions, marketed products…etc**."	To clarify the definition of the study drug and to follow the common protocol template structure.
6.1 Study Interventions Administered	Name: Recombinant anti-PD-1 humanized monoclonal antibody injection (HLX10) **Formulations: Liquid** Specifications: 100 mg (10 mL)/vial	To clarify the formulation of the study drug.
6.2 Dosing Regimen Preparation/Handling/Storage/Accountability	Investigational/reference product: • HLX10: 4.5 mg/kg, IV infusion for 30 to 90 minutes, administered on Day 1 of each cycle, once every 3 weeks (21 days). • Placebo: IV infusion, administered on Day 1 of each cycle, once every 3 weeks (21 days). **The infusion of study drug is completed between 30 mins and 90 mins if there is not any infusion reaction.**	To define the completion of study drug infusion duration.
6.3 Measure to Minimize Bias: Randomization and Blinding	1.Inserted the new header of Section 6.3 **Measure to Minimize Bias: Randomization and Blinding** and description started from **"All subjects will be centrally randomized the IWRS/IVRS. Each subject will be assigned a unique number (randomization number)…etc.'** 2. Inserted subtitle of **Blinding** and the description started from. **" The blinding will be performed by the Data Management and Statistical Unit during study treatment…etc."**	To clarify the randomizing and blinding procedure to minimize bias.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
6.7 Intervention After the End of the Study	Inserted the new header of Section 6.7: **Intervention After the End of the Study** and description started from **"Subjects will receive standard of care…etc."**	To clarify the treatment subject will receive after the completion of the study and to follow the common protocol template structure.
7. Discontinuation of Study Intervention and Participant Discontinuation	Inserted the section 7.2 and 7.3. **7.2 Participant Discontinuation/Withdrawal from the Study** **7.3 Loss of Participants to Follow-Up**	To clarify the discontinuation/ withdrawal, and lost to follow- up from the Study.
8.1 Tests and Evaluations during the Study Table 5 and footnotes	Routine blood test • Basophils **(BAS&BAS%)** • Eosinophils **(EOS&EOS%)** • Lymphocytes **(LYM&LYM%)** • Monocytes **(MON&MONO%)** • Neutrophils **(NEU&NEUT%)** Biochemistry • **Fasting blood glucose (GLU)** Urinalysis • ~~Urine~~ Specific gravity (SG) • **Urine leukocytes** • Urine pH **value** • Urine protein **(U PRO)** • Urinary glucose **(U GLU)** • Ketones **(KET**) • Urine occult blood **(BLO)** • Microscopic examination of white blood cells **(U-WBC)** • Microscopic examination of red blood cells **(U-RBC)** Coagulation function • **Prothrombin time (PT) or** international normalized ratio (INR)	To update Table 5 and footnotes to clarify the variables to be collected during laboratory examination.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	• ~~Activated~~ Partial thromboplastin time (APTT) Footnote c. **Thyroid function tests will be performed during screening and within 3 days prior to drug administration every 2 treatment cycles during the treatment period** ****Routine blood test, blood chemistry, coagulation function and urinalysis must be performed at screening and within 3 days prior to drug administration every treatment cycle. When the aforementioned laboratory tests and study drug administration are scheduled on the same day, the study drug administration must be scheduled only after the test results are obtained. Routine blood tests will be performed on Day 8 (±3 days) of each treatment cycle during treatment with carboplatin, and close attention should be paid to bone marrow suppression.**	
8.1 Tests and Evaluations during the Study Tumor imaging	Imaging studies in this trial include computed tomography or magnetic resonance imaging (CT/MRI). Images will be assessed by the IRRC according to RECIST v1.1 (see Appendix 2-1 **Response Evaluation Criteria in Solid Tumors (RECIST 1.1)**) and ~~modified RECIST~~ **iRECIST** criteria (see Appendix 2-2: **iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics**).	To keep consistent with the study endpoint assessment criteria, changed from "RECIST V1.1 and modified RECIST" to "RECIST V1.1 and iRECIST".
8.1 Tests and Evaluations during the Study Biomarker sample collection	At screening, blood samples **and tumor tissue samples** must be collected for biomarkers detecting. Inserted the description started from: "**Patients must provide tumor tissues that meet the requirements for the determination of PD-L1 expression levels...etc."**	To update the requirement of tissue collection according to inclusion criteria #7.

Section # and Name	Description of Change(s) (*new text is in bold and underlined, deleted text is struck-through)*	Brief Rationale
	Deleted the description started from: ~~"As far as possible, FFPE tumor samples…etc.~~"	
9.3 Populations for Analyses	The definition of the enrolled population was added. Definition wordings of other populations including ITT set, PPS, SS and PKS were re-organized.	To clarify and define the populations to be analyzed in the study.
9.5 Interim Analysis	Wordings were re-organized.	To clarify the definition of the interim analysis.
9.5.1 Independent Data Monitoring Committee (IDMC) 10.1.3 Financial Disclosure 10.1.11 Source Documents 10.1.14 Protocol Approval and Amendment	Several sections were added.	To adhere to the ICH guidance.
10.2 Appendix 1	The version of Common Terminology Criteria for Adverse Events (CTCAE) is updated from v4.03 to v5.	To update the version of CTCAE.
10.5 Appendix 3	Quality of Life Scale EORTC QLQ-C30, EQ-5D-5L and EORTC QLQ-LC13 are updated.	To update the Quality of Life Scale.
Throughout the protocol	Some editorial changes were made.	To keep the consistency throughout protocol.

Shanghai Henlius Biotech, Inc.

HLX10-005-SCLC301

A Randomized, Double-Blind, Multicenter, Phase III Study to Compare Clinical Efficacy and Safety of HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin-Etoposide) in Previously Untreated Patients with Extensive Stage Small Cell Lung Cancer (ES-SCLC)

Statistical Analysis Plan

Version: 1.0_30Nov2021

SPONSOR SIGNATURE PAGE

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TABLE OF CONTENTS

SPONSOR SIGNATURE PAGE 2
TABLE OF CONTENTS 3
REVISION HISTORY 5
LIST OF ABBREVIATIONS 6
1 INTRODUCTION 8
2 STUDY OBJECTIVES 9
2.1 PRIMARY OBJECTIVE 9
2.2 SECONDARY OBJECTIVE(S) 9
3 INVESTIGATIONAL PLAN 9
3.1 OVERALL STUDY DESIGN AND PLAN 9
3.2 ENDPOINTS 14
3.2.1 Efficacy Endpoints 14
3.2.2 Safety Endpoints 16
3.2.3 Pharmacokinetics Endpoint 17
3.2.4 Immunogenicity Endpoint 17
3.2.5 Biomarker Endpoint 17
3.2.6 Quality of life (QoL) Endpoint 17
4 STATISTICAL METHODS 17
4.1 DATA QUALITY ASSURANCE 17
4.2 GENERAL PRESENTATION CONSIDERATIONS 18
4.2.1 Baseline 18
4.2.2 Reference Start Date and Study Day 18
4.2.3 Dosing Window 18
4.2.4 End of Treatment/End of Study 18
4.2.5 Unscheduled Visits 19
4.2.6 Continuous Data 19
4.2.7 Categorical Data 19
4.2.8 Survival Analyses 19
4.2.9 P-values and 95% Confidence Intervals 19
4.2.10 Missing Data Handling 20
4.2.11 Software 20
4.3 ANALYSIS SETS 20
4.3.1 Enrolled Population 20
4.3.2 Intent-to-Treat Population (ITT) 20
4.3.3 Per Protocol Set (PPS) 20
4.3.4 Safety Set (SS) 20
4.3.5 Pharmacokinetics Set (PKS) 21
4.4 STUDY SUBJECTS 21
4.4.1 Disposition of Subjects 21
4.4.2 Protocol Deviations 21
4.5 DEMOGRAPHIC AND BASELINE CHARACTERISTICS 22
4.6 MEDICAL HISTORY 22
4.7 PRIOR AND CONCOMITANT MEDICATION AND PROCEDURE 22
4.8 ANTI-CANCER HISTORY 23
4.9 TUMOR ASSESSMENT 24
4.9.1 Response Assessment (RECIST 1.1) 24
4.9.2 Response Assessment (iRECIST) 24

4.9.3 Imaging Data Status 25
4.9.4 Target Lesion Assessment 25
4.9.5 Non-Target Lesion Assessment 25
4.9.6 New Lesion Assessment 25
4.10 TREATMENT EXPOSURE AND COMPLIANCE 25
4.10.1 Treatment Exposure 25
4.10.2 Treatment Compliance 26
4.11 EFFICACY EVALUATION 27
4.11.1 Analysis and Data Conventions 27
4.11.2 Primary Efficacy Variable 29
4.11.3 Secondary Efficacy Variables 30
4.12 SAFETY EVALUATION 32
4.12.1 Adverse Events 32
4.12.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events 33
4.12.3 Clinical Laboratory Evaluation 34
4.12.4 Vital Signs, Physical Findings and Other Observations Related to Safety 35
4.13 OTHER ANALYSES 36
4.13.1 Pharmacokinetics 36
4.13.2 Immunogenicity 37
4.13.3 Biomarker Analysis 37
4.13.4 Quality of Life Assessment 38
4.14 SAFETY MONITORING (INDEPENDENT DATA MONITORING COMMITTEE [IDMC]) 40
4.15 DETERMINATION OF SAMPLE SIZE 41
4.16 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS 41
4.17 ANALYSES OF DATA FROM ASIAN AND NON-ASIAN 41

5 INCONSISTENCY FROM PROTOCOL 41

6 REFERENCES 42

7 APPEXDIX 43

7.1 APPENDIX 7. 1 SCHEDULE OF ACTIVITIES 43
7.2 APPENDIX 7. 2 LIST OF LABORATORY TESTS 56
7.3 APPENDIX 7. 3 ECOG PERFORMANCE STATUS SCORE 58
7.4 APPENDIX 7. 4 SCORING THE QLQ-C30 VERSION 3.0 59
7.5 APPENDIX 7. 5 SCORING THE QLQ-LC13 62
7.6 APPENDIX 7. 6 TEAE PARTIAL DATE CONVENTIONS 63

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	30Nov2021	Final version

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
ADA	Anti-drug antibody
AE	Adverse Event
AUC	Area under the curve
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete Response
CRF	Case Report Form
CV	Coefficient of variation
DOR	Duration of Response
DRM	Data Review Meeting
ECG	Electrocardiogram
EOCG	Eastern Cooperative Oncology Group
ES-SCLC	Extensive stage small cell lung cancer
EQ-5D-5L	5-level EQ-5D version
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Scale
EoS	End of Study
EoT	End of Treatment
ICF	Informed Consent Form
iCPD	Immune Confirmed Progressive Disease
iUPD	Immune Unconfirmed Progressive Disease
IP	Investigational Product
iRECIST	Modified RECIST 1.1 for immune-based therapeutics
IRRC	Independent Radiology Review Committee
MedDRA	Medical Dictionary for Regulatory Activities
MSI	Microsatellite instability
NA	Not available
NE	Not evaluable
ORR	Objective Response Rate
OS	Overall Survival
QoL	Quality of Life
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PFS	Progression-free Survival
PR	Partial Response

Abbreviation / Acronym	Definition / Expansion
PT	Preferred Term
RECIST 1.1	Response Evaluation Criteria in Solid Tumor guideline, version 1.1
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCLC	Small Cell Lung Cancer
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TLF	Tables, Listings and Figures

1 INTRODUCTION

Small cell lung cancer (SCLC) is derived from epithelial cells with neuroendocrine differentiation, accounting for 15%-20% of the total number of lung cancers. The SCLC is staged using the United States (US) Veterans Administration staging system and is divided into a limited stage and an extensive stage. Most patients present with tumor metastases as the first symptom, and only 30% to 40% of patients are in the limited stage at the time of initial diagnosis. Patients with extensive disease have shorter survival due to extensive tumor metastasis and poor physical status only with supportive care. The median survival time of untreated extensive small-cell lung cancer (ES-SCLC) is reported to be 2-4 months. With a combination of surgery, radiotherapy and chemotherapy, the median survival of ES-SCLC patients can reach 8 to 13 months, with a 2-year survival rate of 5%.

Based on the considerable benefits of PD-1(Programmed cell death 1)/PD-L1(Programmed cell death-ligand 1) inhibitors in patients with tumors, Shanghai Henlius Biotech, Inc. has developed an innovative monoclonal antibody HLX10 targeting PD-1. Based on preclinical animal studies of HLX10, it has the potential to treat a variety of different tumor types, either as monotherapy or in combination with chemotherapy. The present study is planned in previously untreated patients with ES-SCLC worldwide to compare clinical efficacy and safety of HLX10 (recombinant anti-PD-1 humanized monoclonal antibody injection) in combination with chemotherapy (Carboplatin-Etoposide).

This Statistical Analysis Plan (SAP) describes the detailed statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for Tables, Listings and Figures (TLF). It includes the variables and analysis dataset, and manipulations as well as other types of analyses that was not mentioned in the protocol.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 4.0 (05Feb2021)
- Case Report Form (CRF), Version 6.0 (27Jul2021)
- Medical Dictionary for Regulatory Activities (MedDRA), Version 24.0
- World Health Organization’s Drug Dictionary, WHODrug Global Mar2021

2 STUDY OBJECTIVES

2.1 Primary Objective

- To compare the clinical efficacy of HLX10 in combination with chemotherapy versus placebo in combination with chemotherapy in previously untreated patients with ES-SCLC.

2.2 Secondary Objective(s)

- To compare the safety and tolerability of HLX10 in combination with chemotherapy versus placebo in combination with chemotherapy in previously untreated patients with ES-SCLC.
- To measure the exposure following HLX10 administration.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, multicenter, clinical phase III study to compare the clinical efficacy, safety and tolerability of recombinant humanized anti-PD-1 monoclonal antibody injection (HLX10) or placebo in combination with chemotherapy in patients with previously untreated ES-SCLC, to collect PK parameters and to investigate the biomarker related to efficacy. See **Figure 1, Figure 2** for study schema and **Appendix 7. 1** for Schedule of Activities.

Approximately 567 (378 for HLX10 and 189 for placebo) subjects will be randomized to arm A or B at 2:1 ratio in this study as follows:

- **Arm A (HLX10):** HLX10 + Chemotherapy (Carboplatin-Etoposide)
- **Arm B (Control):** Placebo + Chemotherapy (Carboplatin-Etoposide)

Subjects will be randomized and stratified by:

- PD-L1 expression level (negative: tumor proportion scores [TPS] <1%, positive: TPS ≥ 1%, or not evaluable/not available)
- Brain metastasis (yes vs. no)
- Age (≥ 65 years vs. < 65 years)

After screening, subjects meeting the inclusion criteria and not meeting the exclusion criteria will be enrolled. Included subjects will be treated with HLX10 or placebo in combination with chemotherapy once every 3 weeks, until disease progression, death, intolerable toxicity, withdrawal of informed consent, or occurrence of other reasons specified in the protocol (whichever occurs first).

Initial treatment should be discontinued when they have evidence of disease progression as assessed per RECIST 1.1. However, considering the limited availability and efficacy or greater toxicity of treatment options after withdrawal, and for better adaptation to standard clinical practice,

the subjects who meet the following conditions may continue the treatment after appropriate discussion with the subject and obtaining the supplementary informed consent.

1. Subjects who had received HLX10 or placebo in combination with chemotherapy, and who may benefit from continuing HLX10/placebo treatment despite progression, will be able to receive HLX10 or placebo therapy in the post-PD treatment.

2. Subjects eligible for continued treatment in the post-PD treatment period, as judged by the investigator.

3. The subject should sign the supplementary informed consent form to receive investigational product with 2nd line chemotherapy.

4. The subject is clinically stable, defined as:

   a) With no clinical signs and/or symptoms (including worsening of laboratory findings) that might indicate disease progression.

   b) A stable Eastern Cooperative Oncology Group (ECOG) performance status score.

   c) No rapid disease progression or tumor progression requiring urgent alternative medical intervention at critical anatomical sites (e.g., spinal cord compression).

Treatment Groups and Duration:

This study is divided into three periods:

- **Screening period**: maximum 28 days.
- **Treatment period:** initial treatment and post-PD treatment [Optional], until disease progression, death, intolerable toxicity, withdrawal of informed consent, or occurrence of other reasons specified in the protocol, whichever occurs first. After finishing the initial treatment period, patients in both arms who had 1st disease progression per RECIST 1.1 and might benefit from their assigned treatment in addition to 2nd line chemotherapy may be eligible to continue to receive their assigned treatment in the post-PD treatment period (Optional) until the 2nd disease progression, intolerable toxicity, death, withdrawal of consent, or lost to follow-up.
- **Follow-up period** (including safety follow-up and survival follow-up): Safety visit is required at the site 30 days (±7 days) after the last study drug administration, and telephone follow-up is required 90 days (±7 days) after the last study drug administration. Survival follow-up period is every 12 weeks ± 7 days.

The study drugs including HLX10/placebo and chemotherapy drugs are administered every 3-week (21-day) cycle as follows:

Investigational Product: HLX10 or placebo

- **HLX10**: Intravenous (IV) infusion, 4.5 mg/kg, administered on Day 1 of each 3-week (21 day) cycle.

- **Placebo:** Injection is not externally recognizable and contains no HLX10 active ingredient, IV infusion, administered on Day 1 of each cycle, once every 3 weeks (21 days).

The infusion of investigational product is completed between 30 mins and 90 mins if there is not any infusion reaction.

Other Study Drugs: Combined Chemotherapy

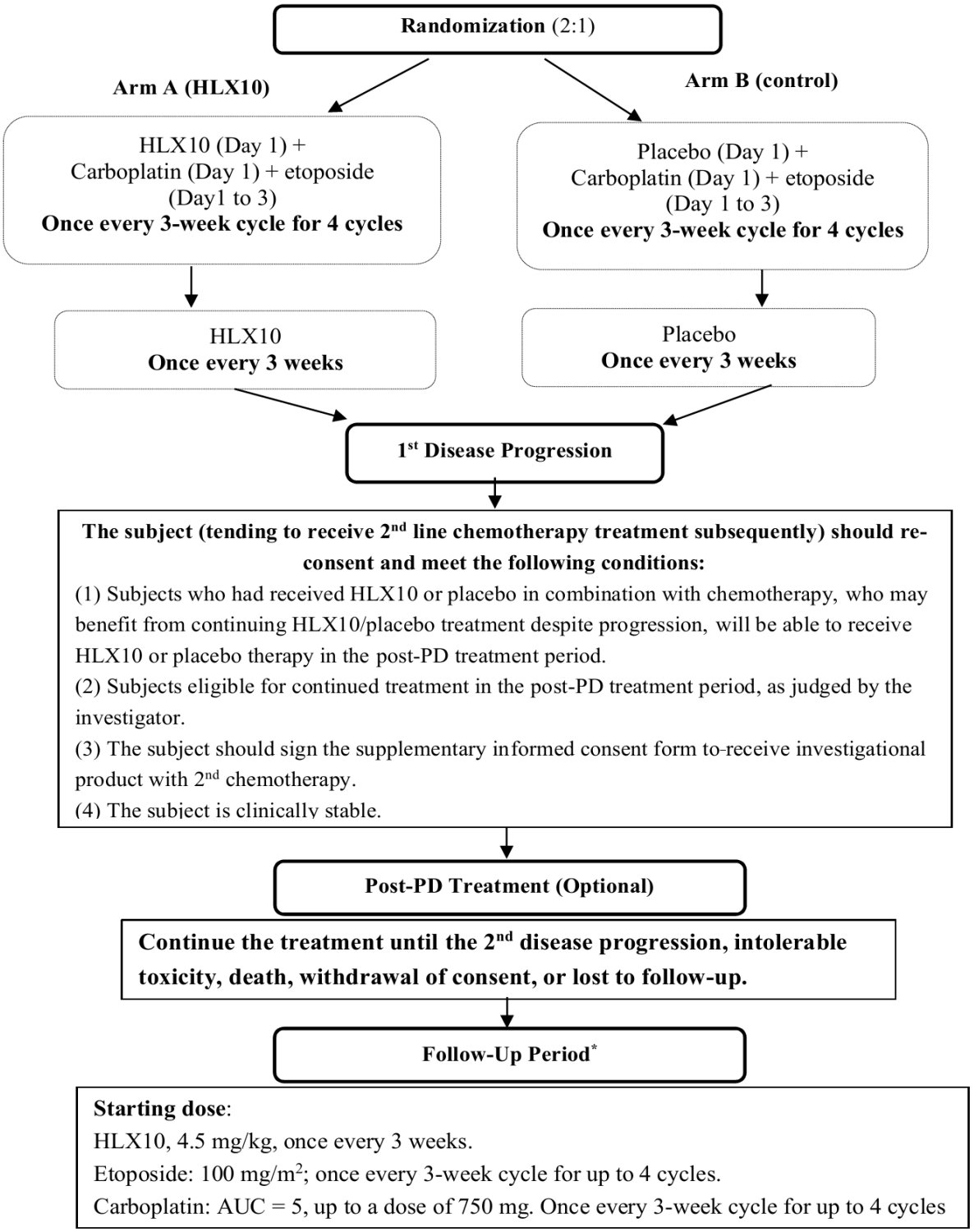
The following regimen will be given every 21-day (3-week) cycle for a maximum of 4 cycles.

- **Etoposide**: 100 mg/m^2, IV infusion, on Days 1, 2, and 3 of each cycle.
- **Carboplatin**: Area under the concentration-time curve (AUC) = 5, IV infusion, on Day 1 of each cycle up to a dose of 750 mg.

Refer to **Figure 1** "Schematic of study treatment" for the regimen of each treatment arm. On Day 1 of dosing in each treatment cycle, subjects will be given HLX10 or placebo intravenously first, followed by intravenous Carboplatin + Etoposide. Vital signs will be closely monitored during the administration. HLX10 or placebo is administered via a blinded infusion, Carboplatin + Etoposide (up to 4 cycles) via an open-label infusion, and subjects will continue receiving Etoposide on Days 2 and 3. Treatment with study drug will continue until disease progression, intolerable toxicity, discontinuation decided by subject or investigator, death, withdrawal of informed consent, pregnancy, noncompliance with protocol or procedure requirements, administrative reasons, or other reasons specified in the protocol, whichever occurs first.

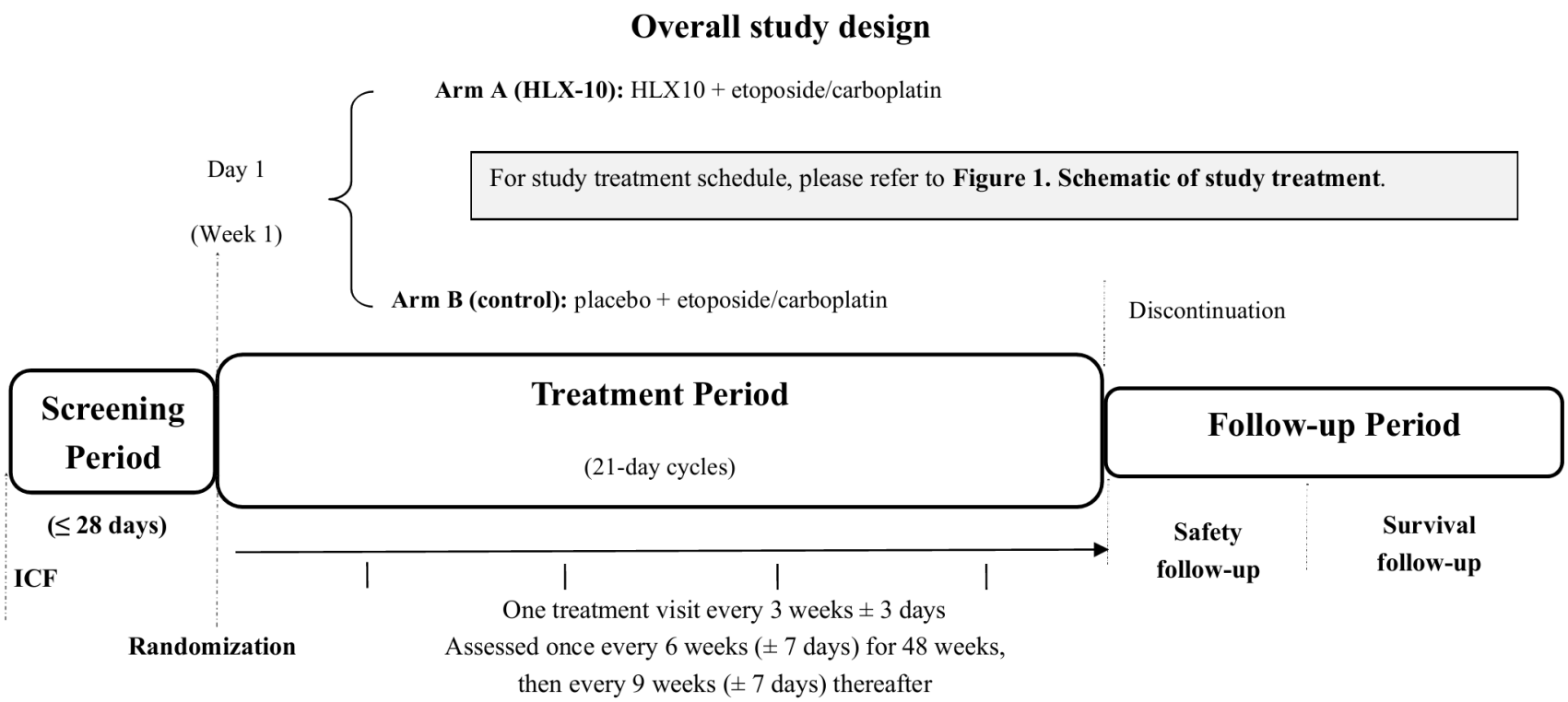
If chemotherapy is not used due to toxicity or other reasons in a certain cycle, it is not counted as the number of chemotherapy cycles. After completing 4 cycles of chemotherapy, even if the subject does not meet the above criteria, the chemotherapy will not be continued.

Figure 1. Schematic of Study Treatment



* Follow-Up Period includes safety follow-up and survival follow-up. Patients who are not eligible for post-PD treatment will be followed up for safety and survival status.

Figure 2. Overall Study Design



Stratification factors:

- PD-L1 expression level (negative: TPS <1%, positive: TPS ≥1%, or not evaluable/not available)
- Brain metastasis (yes versus no)
- Age (≥ 65 years versus < 65 years)

TPS = Tumor Proportion Scores.

Screening period: The maximum screening period is 28 days.
Treatment period: Including initial treatment and post-PD treatment (optional)
After finishing the initial treatment period, patients in both arms who had 1st disease progression per RECIST 1.1 and might benefit from their assigned treatment in addition to 2nd line chemotherapy, may be eligible to continue to receive their assigned treatment in the post-PD treatment period (Optional) until the 2nd disease progression, intolerable toxicity, death, withdrawal of consent, or lost to follow-up.
Safety follow-up period: 90 days after the last study drug administration. Safety visit is required at the site 30 days (±7 days) after the last study drug administration, and telephone follow-up is required 90 days (±7 days) after the last study drug administration.
Survival follow-up period: Every 12 weeks ± 7 days.

3.2 Endpoints

3.2.1 Efficacy Endpoints

Primary Efficacy Endpoint

- Overall survival (OS)

Secondary Efficacy Endpoints

- Progression-free survival (PFS) (assessed by the independent radiology review committee [IRRC] based on Response Evaluation Criteria in Solid Tumors [RECIST] 1.1)
- PFS (assessed by the investigator based on RECIST 1.1 and iRECIST)
- PFS2 (assessed by the investigator based on RECIST 1.1)
- Objective response rate (ORR) (assessed by the IRRC and investigator based on RECIST 1.1)
- Duration of response (DOR) (assessed by the IRRC and the investigator based on RECIST 1.1)

3.2.1.1 Efficacy Variables

Efficacy assessment variables include overall survival (OS), progression-free survival (PFS), progression-free survival 2 (PFS2), objective response rate (ORR) and duration of response (DOR). PFS will be evaluated based on tumor response assessed by IRRC using RECIST 1.1 and by the investigator using RECIST 1.1 and iRECIST; PFS2 will be evaluated based on tumor response assessed by the investigator using RECIST 1.1; ORR and DOR will be assessed by RECIST 1.1 only. The final results of tumor assessment will be determined by IRRC, and the results of the investigator's assessment shall be used as a reference. RECIST1.1 and iRECIST are summarized below:

3.2.1.1.1 RECIST 1.1

RECIST 1.1 will be used to define the overall tumor response based on the response statuses in target lesion, non-target lesion and new lesion for each assessment time point. The overall tumor response can be classified as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE).

3.2.1.1.2 iRECIST

iRECIST was developed by the RECIST working group for the use of modified RECIST 1.1 in cancer immunotherapy trials, to ensure consistent design and data collection, facilitate the ongoing collection of trial data, and ultimate validation of the guideline. iRECIST is based on RECIST 1.1. Responses assigned using iRECIST have a prefix of "i" (i.e., immune), e.g., "immune" complete response (iCR) or partial response (iPR), and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD) to differentiate them from responses assigned using RECIST 1.1. Similar nomenclature is used for stable disease (iSD). New lesions are assessed and

subcategorized into those that qualify as target lesions (new lesion, target) or non-target lesions (new lesion, non-target).

3.2.1.1.3 Overall Survival (OS)

OS is defined as a period from randomization through death regardless of causality. Data of patients without a death record will be censored on the last known survival date.

The between-group comparison of OS is performed by a stratified log-rank test with the following stratification factors: PD-L1 expression level (negative: TPS <1%, positive: TPS ≥1%, or not evaluable/not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years); a stratified COX proportional risk model will be used to estimate HR and its 95% CI; the Kaplan-Meier method will be used to estimate the median, and the Kaplan–Meier curve will be plotted.

3.2.1.1.4 Progression Free Survival (PFS)

PFS is defined as a period from randomization initiation to the first documentation of PD or death regardless of causality (whichever occurs first). Data of subjects with neither PD nor death will be censored on the day of the final valid tumor evaluation. Data of surviving subjects not undergoing any tumor assessment during the study will be censored on the day of randomization. Data of subjects who have no PD reported and initiate any antitumor therapy not specified in the protocol will be censored on the day of the last evaluable tumor assessment prior to the initiation of subsequent antitumor treatment. The PFS will be analyzed using the same method as that for primary endpoints.

PFS assessed by the IRRC and investigator based on RECIST 1.1

According to RECIST 1.1, the PFS is defined as the time from randomization to the time of the first recorded PD or death due to any cause (whichever occurs first). IRRC will be a third-party company designated by the Sponsor for central imaging assessment. The investigator's assessment will be recorded in CRF.

PFS assessed by the investigator based on iRECIST

According to iRECIST, the PFS is defined as the time from randomization to the time of the first recorded iUPD (Immune unconfirmed progressive disease) that is subsequently confirmed (at 4-8 weeks) or death due to any cause (whichever occurs first). If iUPD occurs, but is disregarded because of later iSD, iPR or iCR, that iUPD date should not be used as the progression event date.

3.2.1.1.5 Progression-Free Survival 2 (PFS2)

Progression-free survival 2 (assessed by the investigator based on RECIST 1.1).

PFS2 is defined as the time from randomization to objective tumor progression on next-line treatment or death from any cause. It will be analyzed using the same method as that for PFS.

3.2.1.1.6 Objective Response Rate (ORR)

ORR assessed by the IRRC and investigator based on RECIST 1.1

The ORR is defined as the proportion of subjects with a best overall response of CR or PR, according to RECIST 1.1. The best overall response will be defined as the best response across all time points in the order of CR, PR, SD, PD, and not NE.

3.2.1.1.7 Duration of response (DOR)

DOR assessed by the IRRC and investigator based on RECIST 1.1

DOR is defined as a period from the first documentation of response (CR or PR) through the first documentation of PD or death (whichever occurs first). The DOR will be analyzed only for patients whose best overall responses are evaluated as CR or PR. Data of patients not experiencing PD or death after achieving response will be censored on the day of the final tumor assessment; if no tumor assessment is performed after response achievement, then data of such patients will be censored on the day of tumor assessment when response is achieved. The Kaplan-Meier method is used to estimate the median and plot the Kaplan-Meier curve.

3.2.2 Safety Endpoints

Adverse events (AEs) (including serious adverse events [SAEs]), laboratory tests (routine blood test, blood chemistry, coagulation function, urinalysis, myocardial function and thyroid function), 12-lead electrocardiogram (12 lead ECG), vital signs, and physical examination, etc.

3.2.2.1 Safety Variables

Safety assessments variables include AEs (including SAEs), laboratory tests (routine blood test, blood chemistry test, coagulation test, routine urine test, myocardial function and thyroid function test), 12 lead ECG, vital signs, and physical examination. The timing of all such assessments could be referred to **Appendix 7. 1**.

3.2.2.1.1 Adverse Event

AE is defined as an untoward medical event that occurs after a subject receives a drug, regardless of whether or not it is related to the study drug. AE will be described by MedDRA terms and graded in accordance with CTCAE v5.0. Serious adverse event (SAE), immune-related adverse event (irAE) and death will be collected in the adverse event CRF page. The progression of the underlying disease, that is, the underlying tumor, is not reported as AE, but the occurrence of new tumors should be considered as an SAE.

A treatment-emergent adverse event (TEAE) is defined as an AE that begins or increases in severity or frequency at or after the first study drug administration through end of study (EOS).

Adverse event of special interest (AESI) is defined as an AE of scientific and medical concern related to the use of the study drug that may need to be closely monitored and communicated to sponsors by investigators. In this study, AESIs include infusion reactions (infusion-related adverse reactions, IRRs) and immune-related adverse events (irAEs).

3.2.2.1.2 Laboratory Tests

Laboratory test variables will be collected through routine blood test, serum biochemistry, coagulation, myocardial function, urinalysis, thyroid function, virology, tuberculosis screening (as requested by the Bulgarian Drug Agency for Bulgarian subjects) and pregnancy test. The details can be referred to **Appendix 7. 2**.

3.2.2.1.3 Vital Signs

Vital sign variables will include height, weight, systolic and diastolic blood pressure, pulse, body temperature and respiratory rate.

3.2.2.1.4 Physical Examinations

Physical examination variables will include the results of following examination: head and neck (including thyroid), chest (including heart and lungs), abdomen (including liver, gallbladder, spleen and kidney), limbs, skin, lymph nodes, neurological system and general appearance.

3.2.2.1.5 12-Lead Electrocardiograms

12-Lead ECG variables will include heart rate, RR interval, PR interval, QRS interval, QT interval, QTc interval with Fridericia's formula and overall assessment.

3.2.2.1.6 Eastern Cooperative Oncology Group (ECOG)

ECOG performance status is a grading scale ranging from 0 to 5. Each grade of ECOG performance status can be referred to **Appendix 7. 3**.

3.2.3 Pharmacokinetics Endpoint

The pharmacokinetics (PK) samples of HLX10 will be collected from all subjects and descriptive statistics will be presented for PK concentrations

3.2.4 Immunogenicity Endpoint

Anti-drug antibody (ADA) samples of HLX10 will be collected and the positive rate will be summarized.

3.2.5 Biomarker Endpoint

Relationship between PD-L1 expression, microsatellite instability (MSI), tumor mutation burden (TMB) in tumor tissue and efficacy will be presented in biomarker analysis.

3.2.6 Quality of life (QoL) Endpoint

The health status and self-perceived health of each patient will be documented in the form of EQ-5D-5L scale, EORTC QLQ-C30 scale, and EORTC QLQ-LC13 scale.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

The Sponsor or Sponsor's designee will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded on eCRF for this study must be consistent with the patients' source documentation (i.e., medical records).

All tables, figures and data listings to be included in the report will be independently checked for consistency and integrity.

4.2 General Presentation Considerations

4.2.1 Baseline

The last non-missing measurement prior to the first investigational product (IP) administration will be used as the baseline measurement for all safety and efficacy analysis.

4.2.2 Reference Start Date and Study Day

Reference start date is defined as the day of the first administration of IP in Treatment Period, (Day 1 is the day of the first dose of study treatment in Treatment Period), and study day relative to the reference start date will appear in every listing where an assessment date or event date appears.

Study day will be calculated from the reference start date and will be used to show start/stop day of the assessments and events relative to the first administration of study treatment.

- If the date of the event is on or after the reference date, then:
  Study day = (date of event – reference start date) + 1.

- If the date of the event is prior to the reference date, then:
  Study day = (date of event – reference start date).

For AE where the event date is partial or missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started prior to the first dose of study treatment.

4.2.3 Dosing Window

Dosing window is defined as the scheduled dosing date (calculated based on the first dosing date) ± 3 days. If the dosing window is exceeded, it should be deemed as ‘dose delay’, and subsequent doses shall be administered according to the actual date of last administration.

If a delay of more than 2 weeks is expected due to the toxicity of chemotherapy, only HLX10 or placebo will be administered until the toxicity returns to the standard of chemotherapy administration. Chemotherapy may be continuously suspended for a maximum of 6 weeks, otherwise the chemotherapy should be discontinued.

If a delay of more than 2 weeks is expected due to the toxicity of HLX10 or placebo, only chemotherapy will be administered until the toxicity recovers to the HLX10 or placebo dosing criteria. HLX10 or placebo therapy may be continuously suspended for a maximum of 12 weeks, otherwise the HLX10 or placebo will be discontinued. In case of a delay due to toxicity with equivocal association, all the study drugs shall be synchronously delayed if the event is expected to return to re-dosing standards within 2 weeks.

4.2.4 End of Treatment/End of Study

- End of Treatment (EoT): For any subject withdrawing from the treatment or terminating the treatment regardless of causality, an EOT visit should be performed in 7 days after the end of treatment is learned of or confirmed.

- End of Study (EoS): The end of the study, defined as the final analysis of OS, will be performed when a target number of OS events (approximately 342) are observed, and for final analysis the α is 0.046 (two-sided) based on the O'Brien-Fleming alpha spending function. Or the end of the study is defined as the date when all subjects enrolled completed the safety follow-up 90 days after the end of treatment visit. Whichever occurs first. Additionally, the sponsor may decide to terminate the study at any time.

4.2.5 Unscheduled Visits

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries but will contribute to best/worst case value where required (e.g., shift table).

In the case of a re-test (visit-specific unscheduled visit number assigned), the re-test data will be used for by-visit summaries.

Listings will include the scheduled, unscheduled, re-test, and early discontinuation data.

4.2.6 Continuous Data

Continuous data will be summarized in terms of the mean, standard deviation, median, minimum, maximum and number of observations, unless otherwise stated.

Continuous data that are expected to be skewed will be presented in terms of the maximum, 3rd quartile, median, 1st quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, 1st quartile and 3rd quartile will be reported to one more decimal place than the raw data recorded in the database. The standard deviation will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

4.2.7 Categorical Data

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point, frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using N as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

4.2.8 Survival Analyses

In survival analyses (including PFS, OS and DOR analyses), time-to-event in days will be calculated as (Event Date – Start Date + 1). The duration in days may be converted to months as (12 * Number of Days / 365.25)) or weeks as (Number of Days / 7).

4.2.9 P-values and 95% Confidence Intervals

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Confidence intervals will be presented to one more decimal place than the raw data.

4.2.10 Missing Data Handling

For other unspecified analyses, missing data will not be imputed. In the situation where the event date is partial or missing, the date will appear partial or missing in the listings.

Any AE corresponding durations will be presented based on the imputations specified in **Appendix 7. 6 TEAE Partial Date Conventions**

4.2.11 Software

All report outputs will be produced using SAS® version 9.3 or a later version in a secure and validated environment and provided in Microsoft Word 2016 or a later version document, RTF or PDF format.

4.3 Analysis Sets

The analysis sets of this study are defined as follows.

4.3.1 Enrolled Population

Enrolled Population is defined as all participants who signed the informed consent form (ICF) (including screening failures).

4.3.2 Intent-to-Treat Population (ITT)

The ITT Population comprises all participants to whom study intervention has been randomized. Statistical analyses will be based on study intervention groups as per randomization, irrespective of the study intervention actually received. The ITT Population will serve as the primary population of efficacy assessment in this study. ITT Population will be analyzed based on planned treatment arms.

4.3.3 Per Protocol Set (PPS)

The PPS comprises a subset of the ITT. The PPS consists of all randomized subjects without any major protocol deviation that impacts the primary efficacy significantly. The PPS will be used to demonstrate robustness of results for the primary efficacy endpoint.

The protocol deviations that significantly affect evaluation for the primary efficacy will be determined based on a blinded data review prior to interim/final database lock. Analyses for the PPS will be based on actual treatment received. PPS analysis will supplement the ITT analysis as supporting analysis to demonstrate robustness of results for the efficacy endpoint.

4.3.4 Safety Set (SS)

Safety Set (SS) is defined as all subjects who received at least one dose of study intervention. Participants will be analyzed according to the study intervention they actually received. The safety set is the primary population for safety endpoint analysis.

4.3.5 Pharmacokinetics Set (PKS)

The Pharmacokinetics Set (PKS) consists of all participants who received at least one dose of HLX10 with at least one measurable post-dose concentration at scheduled PK time points without any major protocol violation that may impact the PK assessment significantly. The PK analysis set will be used for PK analysis

4.4 Study Subjects

4.4.1 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion. The following summaries of subject disposition will be provided:

- A summary of the numbers and percentages of subjects screened, who are screen failures, who are randomized, who discontinue study treatment, whose primary reason for treatment discontinuation, who sign the ICF for continuous treatment, who ever received treatment after progressive disease, who completed the study and whose primary reason for study discontinuation by study treatment and overall. (Analysis set: Enrolled Population).
- A cross-table will be presented to show the planned and actual treatment for ITT Population.
- A by-subject listing of disposition will be provided, including subject identifier details, informed consent details (including informed consent for continuous treatment), randomization details, the first/last dosing date, details of end of treatment and end of study (including reason for treatment/study discontinuation) (Analysis set: Enrolled Population).

The following summary will be provided:

- A summary of the number and percentage of subjects entering each analysis set by study treatment and overall (Enrolled Population).
- A summary of the number and percentage of subjects randomized by study treatment, country and site (Analysis set: Intent-to-treat Set).
- A by-subject listing of analysis set details will be provided (Analysis set: Intent-to-treat Set).

The listing will be presented by planned arm and include: actual arm, country, site, subject identifier, inclusion/exclusion flag for each analysis set and reason for exclusion from each analysis set (Analysis set: Intent-to-treat Set).

4.4.2 Protocol Deviations

Protocol deviations including those deviations from the protocol that will be assessed as “Major”, “Major COVID-19”, “Minor” or “Minor COVID-19” in collaboration with Sponsor.

Significant major deviations, which are defined as those major protocol deviations leading to exclusion from analysis sets, will be defined in a Data Review Meeting (DRM) shortly prior to the interim/final database lock. Results and population assignments will be summarized in a DRM report signed off by all relevant team leaders.

The following summary will be provided:

- A summary of the number and percentage of subjects with a major protocol deviation by type of deviation and study treatment (Analysis set: Intent-to-treat Set)
- A by-subject listing of major/ major COVID-19/ minor/ minor COVID-19 protocol deviations will be provided (Listing analysis set: Intent-to-treat Set).

4.5 Demographic and Baseline Characteristics

Subject demographic, baseline characteristics, and randomization stratification factors will be summarized descriptively by study treatment in ITT Set. The following demographics and baseline characteristics and stratification factors will be summarized:

- Demographic variables: Age, Sex, Childbearing potential for female, Race, Ethnicity, Height, Weight, and Body mass index.

  Age (years): (date of given informed consent – date of birth + 1) / 365.25. The integer part of the calculated age will be used for reporting purpose.

- Baseline characteristic variables: ECOG, biomarker assessment (MSI, TMB), anti-HIV assessment, anti-HCV assessment, History of smoking, Alcohol consumption, Drug dependence (yes/no) and Allergies (yes/no).
- Stratification factors: PD-L1 expression level (negative, positive, not available), Brain metastasis (yes vs. no), and Age (≥ 65 vs. < 65 years).
- Baseline SCLC characteristics: Time since initial diagnosis (years), VALG stage at initial diagnosis, Overall stage at study entry, VALG stage at study entry, Overall stage at study entry, Metastasis status and Sites of Metastasis.
- Baseline Echocardiogram: LVEF (%), Assessment (Normal, Abnormal - Not Clinically Significant, Abnormal - Clinically Significant).

By-subject listings of demographics as well as baseline characteristics and stratification factors and baseline SCLC characteristic will be provided (Listing analysis set: Intent-to-treat Set).

4.6 Medical History

Patient's medical history including previous and existing clinically significant abnormality, medical conditions, diagnostic results, (drug) sensitivities/allergies, major surgeries and relevant physical examination findings will be recorded in eCRF "Medical History" with CTCAE grade (grade 1 - grade 5).

Medical history are conditions (other than the indication being studied) which started prior to ICF is signed or on the date of screening. Medical history still ongoing at enrolment or ended prior to enrolment will be listed together for the ITT Population. Number and percentage of subjects with any medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) of MedDRA coding system (version 24.0) in the order of frequency for the ITT Population with a corresponding listing (Listing analysis set: Intent-to-treat Set).

4.7 Prior and Concomitant Medication and Procedure

Concomitant medication is any medication other than the IP that is taken from the time of first dose to the end of study. Upon entering the study, each subject will be instructed to report the use

of any medication to the investigator. Prior medication will be recorded up to 30 days before signing the ICF on the eCRF (Form: Prior and Concomitant Medication). All prior and concomitant medications will be listed individually. The prior and concomitant medications will be summarized with the number and percentage of subjects by anatomical main group and pharmacological subgroup using WHODrug Global Mar2021 or higher in the order of frequency for the ITT Population with a corresponding listing.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study medication. If there is clear evidence to suggest that the medication started prior to the first dose of study medication, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior only.

- Medications collected in the CRF "Prior and Concomitant Medication" will be classified as Prior only if they start and stop prior to the date of first dose of study drug.
- If medication start before the date of first dose of study drug and stop on or after the date of first dose of study drug, then they will be classified as both Prior and Concomitant.
- Medications will be classified as Concomitant only if they have a start date on or after the date of first dose of study drug.
- Medications starting after the EOT date will be listed but will not be classified or summarized.

Based on the same classified rule of medication, the procedures collected in the eCRF (Prior and Concomitant Procedures) will also classified as "Prior only", "both Prior and Concomitant" and "Concomitant only".

The following summary will be provided:

- Summary of the classification of medications (Prior only, both Prior and Concomitant, and Concomitant only) by anatomical therapeutic chemical (ATC) and preferred term by Prior only, both Prior and Concomitant, and Concomitant only (Analysis set: Intent-to-treat Set)
- Summary of the classifications of procedure (Prior only, both Prior and Concomitant, and Concomitant only) by SOC and preferred term (Analysis set: Intent-to-treat Set)
- By-subject listings of medication and procedure will be provided respectively (Listing analysis set: Intent-to-treat Set).

4.8 Anti-Cancer History

Anti-cancer procedures, therapy and radiotherapy will be collected for following information (eCRF: Prior Anti-Cancer Surgery or Procedures; Anti-Cancer Surgery or Procedures After Study Drug; Prior Systemic Anti-Cancer Therapy; Anti-Cancer Therapy After Study Drug; Prior Radiotherapy; Concomitant or Post-Treatment Radiotherapy; Anti-Cancer Treatment after First Disease Progression).

- **Prior Anti-Cancer Surgery or Procedures:** Surgery or Procedure Description; Start Date; Stop Date; Category (Major vs. Minor).

- **Prior Systemic Anti-Cancer Therapy:** Regimen number; Type; Line of therapy; Best response; Medication; Start date; End date; Dose; Unit; Frequency; Route.

- **Prior Radiotherapy:** Type of radiotherapy; Anatomical location; Start date; End date; Indication; Total cumulative dose; Progression status of the lesion(s) since the last radiotherapy.

- **Concomitant or Post-Treatment Radiotherapy:** Type of radiotherapy; Anatomical location; Start date; End date; Indication; Total cumulative dose.

- **Anti-Cancer Therapy After Study Drug:** Regimen number; Type; Line of therapy; Medication; Start Date; End Date; Dose; Unit; Frequency; Route.

- **Anti-Cancer Surgery or Procedures After Study Drug:** Surgery or procedure description; Reason for Surgery or Procedure; Date of surgery or procedure; Biopsy location; Biopsy result.

- **Anti-Cancer Treatment after First Disease Progression:** Regimen number; Type; Line of therapy; Medication; Start Date; End Date; Dose; Unit; Frequency; Route.

Overall summary tables will be summarized by SOC and PT separately for the above 7 anti-cancer histories in ITT Population with corresponding listings (Listing analysis set: Intent-to-treat Set).

4.9 Tumor Assessment

4.9.1 Response Assessment (RECIST 1.1)

Response assessment (RECIST 1.1) will be collected for following information (eCRF: Response Assessment (RECIST 1.1)): Date of Assessment; Response of target lesions (CR, PR, PD, SD, NA, NE); Response of non-target lesions (CR, Non-CR/Non-PD, PD, NA, NE); Any new lesion; Overall assessment (CR, PR, SD, PD, NE).

4.9.2 Response Assessment (iRECIST)

Response assessment (iRECIST) will be collected for following information (eCRF: Response Assessment (iRECIST)): Date of Assessment; Response of target lesions (iCR, iPR, iUPD, Non-iUPD/PD, iCPD, iSD, NA, NE); Response of non-target lesions (iCR, Non-iCR/Non-iUPD, iUPD, iCPD, NA, NE); Overall status of new non-target lesions (Present, Improved, Absent/Normal, Unequivocal progression, Not evaluable); Overall assessment (iCR, iPR, iSD, iUPD, iCPD, NE, ND).

4.9.3 Imaging Data Status

Imaging data status will be collected for following information (eCRF: Imaging Data Status): Scan Date; Scan Method (Plain CT, Enhanced CT, MRI, Enhanced MRI, Chest X-ray, Bone Scan, Other); confirmation of scan used for lesion assessment.

4.9.4 Target Lesion Assessment

Target lesion assessments will be collected for following information (eCRF: Target Lesion Assessment): Sum of Diameters (mm) (For Lesions detected at Baseline); Sum of Diameters (mm) (For Lesions detected at Rebaseline); Lesion number; Location; Imaging performed date; and Imaging performed methods; Longest diameter (mm); Short axis (mm).

4.9.5 Non-Target Lesion Assessment

Non-target lesion assessments will be collected for following information (eCRF: Non-Target Lesion Assessment): Lesion number; Location; Imaging performed date; and Imaging performed methods; Status of lesion.

4.9.6 New Lesion Assessment

New lesion assessments will be collected for following information (eCRF: New Lesion Assessment): Lesion number; Location; Imaging performed date; and Imaging performed methods; Measure status of lesion; Target status of lesion; New lesion target longest diameter (mm); New lesion target short axis (mm); Status of new lesion non-target; Sum of diameters (mm); Overall status of new lesion non-target.

The overall summary tables will be summarized between Arm A and Arm B separately for Target lesion, non-target lesion and new lesion assessments in ITT Population with corresponding listings.

4.10 Treatment Exposure and Compliance

4.10.1 Treatment Exposure

Summary statistics will be provided for the actual duration of exposure, actual cumulative total dose received, dose intensity and relative dose intensity by visit and study drugs (HLX10/placebo, Carboplatin and Etoposide) in Safety Set. The exposure indices are defined as follows:

- The planned duration of exposure is defined as the planned number of treatment and it can be calculated as

$$(\text{the last planned dosing date} - \text{the first dosing date} + 1)/7$$

- The actual duration of exposure is defined as the duration from the first dosing date to the last dosing date. Actual duration of exposure (in weeks) will be calculated as

$$(\text{the last dosing date} - \text{the first dosing date} + 1)/7$$

- The actual cumulative total dose received (mg) is defined as the summation of all actual dose administrated from the first dosing date to the last doing date.
- The planned cumulative total dose received (mg) is defined as the summation of all planned dose administrated from the first dosing date to the last planned doing date.
- Planned dose intensity (PDI) and Average dose intensity (ADI) will be calculated as

$$\text{PDI} = \frac{\text{Planned cumulative total dose received}}{\text{Planned duration of exposure}}$$

$$\text{ADI} = \frac{\text{Actual cumulative total dose received}}{\text{Actual duration of exposure}}$$

- Relative dose intensity (RDI) will be defined as

$$\text{RDI} = \frac{\text{ADI}}{\text{PDI}} \times 100\%$$

- Planned dose

  The planned dose of HLX10 is 4.5 mg/kg, on Day 1 of each cycle, once every 3 weeks.

  The planned dose of Etoposide is 100 mg/m^2, on Days 1, 2, and 3 of each cycle.

  Etoposide planned dose = 100 mg/m^2*BSA(m^2).

  The planned dose of Carboplatin is AUC = 5, up to a dose of 750 mg, on Day 1 of each cycle, calculated using the following Calvert formula:

  - Dose of Carboplatin (mg) = target AUC x [(CrCl (mL/min) + 25)]

    where AUC is the target area under the Carboplatin plasma concentration versus time curve and AUC = 5, and CrCl is the estimated creatinine clearance and its calculation is based on the following Cockcroft-Gault formula:

  Male: $[(140 - \text{age in years}) \times \text{body weight (kg)}] / [\text{Serum creatinine} \times k]$

  Female: $[(140 - \text{age in years}) \times \text{body weight (kg)}] / [\text{Serum creatinine} \times k] \times 0.85$

  where k = 72 if the unit of serum creatinine is mg/dL; k = 1/1.23 if the unit of serum creatinine is μmol/L. Maximum dose of Carboplatin ≤ 750 mg if AUC = 5.

  If the change in the subject's body weight from baseline during the study is less than or equal to 10%, dose adjustment of investigational product will not be required; if the weight change is greater than 10%, the dose of investigational product must be recalculated and specified in the planned dose data.

4.10.2 Treatment Compliance

Administration of study drugs (HLX10; Placebo; Carboplatin; Etoposide) will be collected for the following information (eCRF: Administration-HLX10/Placebo; Administration-Carboplatin; Administration-Etoposide): Actual dose (unit); Start date/time; End date/time; Action taken during the infusion; Infusion rate change; Reason for the action taken during the infusion.

Medication compliance of the study drugs be summarized by study treatment using Safety Set. The following summary will be provided:

- Summary of action taken and the reason for the action taken during the HLX10/Placebo infusion with cross tabulation by visit and study treatment. The summary will be presented repeatedly on Carboplatin and Etoposide (Analysis set: Safety Set).

- Summary of infusion rate change HLX10/Placebo by visit and study treatment. The summary will be presented repeatedly on Carboplatin and Etoposide (Analysis set: Safety Set).
- By-subject listings of administration of HLX10/Placebo, Carboplatin, and Etoposide will be provided respectively (Listing analysis set: Safety Set).

4.11 Efficacy Evaluation

Analyses of the primary efficacy endpoint and the secondary efficacy endpoints will be performed for both the ITT and PPS, mainly on the ITT.

4.11.1 Analysis and Data Conventions

This study is designed to test for superiority. For the time-to-event endpoint (e.g., PFS, OS), the null hypothesis (H_0) and the alternative hypothesis (H_1) can be expressed as follows:

$$H_0: S_A(t) = S_B(t) \text{ for all } t$$
$$H_1: S_A(t) \neq S_B(t) \text{ for some } t$$

where $S_A(t)$ and $S_B(t)$ are the rates of time-to-event for Arm A (HLX10 + chemotherapy) and Arm B (Placebo + chemotherapy) at time t, $t > 0$. The comparison of the time-to-event between the two arms will be performed by a two-sided stratified log-rank test and the prespecified stratification factors. Time-to-event distributions will be estimated using the Kaplan-Meier (KM) product-limit method. If median event time is evaluated, the corresponding two-sided 95% confidence interval (CI) will be computed using the Brookmeyer-Crowley approach. The standard error of the survival rate at a fixed time point (e.g. PFS rate at 6 months) will be estimated using Greenwood's formula. The hazard ratio and its 95% CI will be estimated by stratified Cox proportional hazards model. Efron's method will be used to handle ties. All CIs will be presented to one more decimal place than the point estimate.

For binomial proportions endpoints (e.g., ORR), considering the stratified randomization, the stratified Cochran-Mantel-Haenszel method is used to test the between-group variation in the ORR and to estimate the odds ratio and its 95% CI. For each single arm, the 95% CI for the proportion will be derived using Clopper-Pearson method.

Considering the stratified randomization, the stratified Cochran-Mantel-Haenszel method is used to test the between-group variation in the ORR and to estimate the odds ratio and its 95% CI. The estimate for ORR and 95% Clopper-Pearson CI will also be provided.

Any major protocol deviation potentially affecting the efficacy analysis would be discussed in DRM. If there is any doubt about the efficacy data involving major protocol deviation, the efficacy data will be available up to the last efficacy assessment prior to the major protocol deviation

4.11.1.1 Adjustments for Covariates

All analyses of efficacy endpoints will be stratified by PD-L1 expression level (negative: TPS <1%, positive: TPS ≥1%, or not evaluable/not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years). If a subject is assigned in a wrong stratum, he/she will be analyzed per "randomized stratum". A sensitivity analysis will be performed for PFS and OS using "actual stratum".

4.11.1.2 Multiple Comparisons/Multiplicity

One primary variable has been defined for this study, one critical treatment contrast (Arm A vs. Arm B). The secondary variables defined are intended to provide supportive evidence relating to the primary objective and no labeling claims are intended. There is a planned interim analysis whose approach of controlling type I error will be described in the interim analysis section **4.11.1.3**. Hence, except the interim analysis, no adjustments for multiplicity are required.

4.11.1.3 Interim Analyses

This study plans to carry out an interim analysis. An Independent Data Monitoring Committee (IDMC) will be established for the interim analysis. The O'Brien-Fleming type alpha-spending function (using the Lan-DeMets method to approximate) shall be used to control overall type I error rate. The stopping boundary for OS interim and final analyses are shown in Table 1.

Table 1. Analysis Timing and Stopping Boundary of Overall Survival

Analysis Timing	Information Fraction (Number of Events)	Estimated Time (month)	Stopping Boundary (p-value)
OS interim analysis	66% (226)	19	<0.012
OS final analysis	100% (342)	34	<0.046

- The first interim analysis is scheduled to be conducted when 66% (approximately226) of OS events are observed, and the interim analysis will assess the safety and efficacy of the trial group. The α for the first interim analysis will be 0.012 (two-tailed) based on the O'Brien Fleming type alpha-spending function.
- The final analysis of OS will be performed when a target number of OS events (approximately342) are observed, and the α for the final analysis will be 0.046 (two tailed) based on the O'Brien-Fleming type alpha-spending function.

4.11.1.4 Examination of Subgroups

To assess the consistency of the study OS, PFS and PFS2, results in subgroups will be examined. The following subgroups will be considered:

- Age (≥ 65 years vs. < 65 years)
- Sex (Male vs. Female)
- Race (Asian vs. non-Asian)
- Ethnicity (Hispanic of Latino vs. non-Hispanic of Latino)
- Baseline ECOG performance status (0, 1)
- Baseline smoking status
- Baseline brain metastasis (yes vs. no)

To explore the efficacy under different PD-L1 expression level, the following subgroups will be examined.

- PD-L1 expression level based on tumor proportion scores (positive TPS ⩾1% vs. negative TPS <1%)
- PD-L1 expression level based on combined positive score (positive CPS ⩾1% vs. negative CPS < 1%)

Summaries of OS, PFS and PFS2, including unstratified HRs estimated from Cox proportional hazards models will be displayed in a forest plot. Kaplan-Meier estimates of median OS, PFS and PFS2 will be produced separately for each level of the categorical variables for the comparisons between treatment arms.

The survival curve and median survival time will be estimated by Kaplan-Meier approach for subgroups (including: Age, Baseline brain metastasis, PD-L1 expression level based on TPS and CPS). The Brookmeyer-Crowley method will be used to construct the 95% CI for the median survival time.

All the subgroup analyses will be summarized using the ITT Set and Per Protocol Set.

4.11.2 Primary Efficacy Variable

Overall Survival

The primary efficacy endpoint is the OS. OS is defined as the time from randomization to death from any cause. Subjects with no death record will be censored at the last known date of survival. Subjects who did not provide any follow-up information within the study period will be censored on the date of randomization.

If the death year and months is available but date is missing, the 1st day of the month or the latest known alive date will be used to impute the death date, whichever later.

If both month and day are missing for death date or a death date is totally missing, do not impute and censor the subject at the last known alive date.

The comparison of OS between the two arms will be performed by stratified log-rank test at $\alpha = 0.05$ with the following stratification factors: PD-L1 expression level (negative: TPS <1%, positive: TPS ≥1%, or not evaluable/not available), Brain metastasis (yes versus no), Age (≥ 65 years versus < 65 years).

Median OS and OS curve will be estimated using Kaplan-Meier method. The Brookmeyer-Crowley method will be used to construct the 95% CI for the median OS. The standard error of the Kaplan-Meier quartile estimates will be estimated using Greenwood's formula. The hazard ratio and its 95% CI will be estimated by stratified Cox proportional hazards model. Efron's method will be used to handle ties.

The analysis of primary efficacy endpoint will be using ITT Population, and the analysis will be repeated on PPS as a supporting analysis.

The following summary will be provided:

- A summary of the median OS with corresponding two-sided 95% CI by study treatment (Analysis set: ITT set, PPS)

- A summary of the OS rate at 3, 6 and 9 months with corresponding two-sided 95% CI by study treatment (Analysis set: ITT set, PPS)
- A summary of the OS hazard ratio based on the stratified Cox proportional hazards model and the p-value for stratified long-rank test (Analysis set: ITT set, PPS)
- A plot of Kaplan-Meier survival curve with two-sided 95% CI by study treatment (Analysis set: ITT set, PPS)

A by-subject listing of the primary efficacy data will be provided (Listing analysis set: ITT Population).

4.11.3 Secondary Efficacy Variables

4.11.3.1 Progression Free Survival (PFS)

All assessment date will be based on the date of scans. In the instance where there are different dates of scans within the same tumor assessment, the response assessment will use the last scan date where lesions are defined and an assessment of PD, iCPD or iUPD will be dated on the earliest scan date that demonstrates PD.

PFS assessed by the IRRC and investigator based on RECIST 1.1

PFS is defined as the time from randomization to the first recorded PD/death due to any cause (whichever occurs first).

The PFS will be censored based on the following algorithms:

- Subjects without PD/death at the end of study or the cut-off date will be censored at the date of last effective tumor evaluation.
- Subjects who did not undergo any tumor assessment during the study and did not die at the end of study or the cut-off date will be censored on the day of randomization.
- Subjects who had no PD and started anticancer treatment which is not stipulated in the protocol will be censored at the day of the last effective tumor assessment before anticancer treatment.
- Subjects who had a major protocol deviation that is prior to the unblinding and affects the efficacy analysis will be censored at the day of the last effective tumor assessment prior to the day of major protocol deviation. The impact of major protocol deviation on efficacy analysis will be discussed in the DRM.
- Subjects who had the 1st PD assessed by IRRC after the 2nd line anti-cancer therapy will be censored at the day of the last effective tumor assessment prior to the day of 2nd line chemotherapy. This rule only applies to subjects who assigned the 2nd line anti-cancer therapy after 1st PD assessed by investigator.

If PD/death year and month (YYYYMM) are available but day (DD) is missing:

- If YYYYMM for last date of effective tumor assessment where subjects are known to be alive > YYYYMM for PD/death date, then that is a data error and do not impute; otherwise
- set PD/death date to the day after the last date of effective tumor assessment or to the first day of the PD/death month, whichever is later.

If both month and day are missing for PD/death date or a PD/death date is totally missing, do not impute and censor the subject at the last date of effective tumor assessment.

Statistical methods for PFS are the same as those for the primary efficacy endpoint (Analysis set: ITT Set, PPS).

PFS assessed by the investigator based on iRECIST

If iUPD is observed and the subsequent tumor assessment is not done at the following 4-8 weeks or out of the time window, the PFS should be calculated as below:

- If iCPD is less than 4 weeks after iUPD, the iCPD will be disregarded.
- If there are multiple iUPD before the iCPD, the latest iUPD date will be used to calculate PFS.
- If there is iUPD followed by "Death" without any iCPD, the PFS will be treated as an event, and the latest iUPD date before death will be used to calculate PFS.
- If there is no iCPD or "Death" after iUPD, the PFS will be censored to the day of last effective tumor assessment.

Statistical methods are the same PFS based on RECIST 1.1 (Analysis set: ITT Population, PPS).

4.11.3.2 Progression Free Survival 2 (PFS2)

PFS2 is defined as the time from randomization to objective tumor progression on next-line treatment or death from any cause. If a patient dies without any progression events, the patient's PFS and PFS2 event dates would be equivalent. If a patient dies after their primary PFS event, but prior to the initiation of subsequent anti-cancer therapy, their death date is still considered their PFS2 event. Patients alive and for whom a second disease progression has not been observed should be censored at the last tumor assessment date.

PFS2 will be analyzed using the same method as the analysis of PFS (Analysis set: ITT Population, PPS).

4.11.3.3 ORR assessed by the IRRC and investigator based on RECIST 1.1

ORR will be defined as the proportion of subjects with a best overall response of CR or PR as defined by RECIST 1.1 during the study. Subjects without post-baseline tumor assessments will be counted as non-responders in calculating the ORR. Considering the stratified randomization, the stratified Cochran-Mantel-Haenszel method is used to test the between-group variation in the ORR and to estimate the odds ratio and its 95% CI. The estimate for ORR and 95% Clopper-Pearson CI will also be provided.

4.11.3.4 DOR assessed by the IRRC and investigator based on RECIST 1.1

DOR will be defined as the time from the first recorded CR or PR to the first recorded PD or death (whichever occurs first). The tumor responses CR, PR, and PD will follow the definition in RECIST 1.1. DOR will be only analyzed for subjects who achieved CR or PR best overall response. Subjects who do not experience PD or death after the first CR or PR will be censored on the final

tumor assessment day; Subjects who had no any tumor assessment after achieving the first CR or PR will be censored on the day of achieving the first CR or PR. The Kaplan-Meier method is used to estimate the median and plot the Kaplan-Meier curve (Analysis set: ITT Set, PPS).

A by-subject listing of the secondary efficacy data will be provided (Listing analysis set: ITT Population).

4.12 Safety Evaluation

Safety evaluation is often based upon summaries of the data rather than formal statistical inference. All safety summaries and analyses will be based upon the Safety Set (SS).

4.12.1 Adverse Events

All AEs will be coded using the latest version of MedDRAcoding system.

If an AE is reported for a given subject more than once for a period, the worst severity and the strongest relationship to study treatment will be used for that period.

All the records belonging to the same AE set will be kept in the analysis datasets as separate records

- If an AE started before treatment start and improved during treatment, it should not be counted as TEAE
- If an AE worsened during the treatment period, it is counted as TEAE even if there was an observation with start date before treatment period.

Adverse events with relationship “Related”, “Possibly Related” and “Unknown” will be classified as “Related” with the study drug.

An overall summary table of the following AEs will describe the number of events, number of subjects with events and incidence rate and also be tabulated by SOC and PT.

- **Incidence** = $\frac{(\text{Number of Subject with TEAE})}{\text{Number of subjects in the Safety Set}}$

- AEs
- TEAEs
- TEAEs by Severity (Grade1, 2, 3, 4 and 5)
- Related TEAEs
- Grade ≥ 3 TEAEs
- Related Grade ≥ 3 TEAEs
- TEAEs leading to discontinuation of study drugs (HLX10/Placebo)
- Related TEAEs leading to discontinuation of study drugs (HLX10/Placebo)
- TEAEs leading to discontinuation of Carboplatin
- Related TEAEs leading to discontinuation of Carboplatin
- TEAEs leading to discontinuation of Etoposide

- Related TEAEs leading to discontinuation of Etoposide
- TEAEs leading to interruption of study drugs (HLX10/Placebo)
- Related TEAEs leading to interruption of study drugs (HLX10/Placebo)
- TEAEs leading to interruption of Carboplatin
- Related TEAEs leading to interruption of Carboplatin
- TEAEs leading to interruption of Etoposide
- Related TEAEs leading to interruption of Etoposide

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, in Arm A (HLX10 + chemotherapy), and then similarly by decreasing frequency in Arm B (Placebo + chemotherapy), and then alphabetically for SOC, and PT within SOC treatment (Analysis set: Safety Set).

A by-subject listing of all AEs (including non-treatment-emergent events) will be provided (Listing analysis set: Safety Set).

4.12.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

4.12.2.1 Death

All deaths that occur during the study or the follow-up period after the final dose of study drug as specified in the protocol must be reported in accordance with the requirements in the protocol. The following summary will be provided:

- A summary of the number and percentage of deaths during the study, by study treatment and overall (Analysis set: Safety Set).
- A by-subject listing of all deaths (Listing analysis set: Safety Set).

4.12.2.2 Serious Adverse Event and Immune-related Adverse Event

All AEs that meet any one or more of the following situations during the clinical trial should be considered SAE:

1. Leading to death
2. Life-threatening
3. Hospitalization (initial or prolonged)
4. Permanent or severe disability/dysfunction
5. Congenital anomaly or birth defect
6. Other important Medical Events

The treatment-emergent serious AE (TESAE) is an SAE which is also treatment-emergent. The present of SAE and immune-related adverse event (irAE) are collected in the CRF. Subject incidence of the following SAEs, TESAEs and irAEs will be tabulated by study treatment, SOC and PT treatment (Analysis set: Safety Set):

- TESAEs

- Related TESAEs
- TESAEs leading to discontinuation of study drugs
- TESAEs leading to discontinuation of any component of chemotherapy
- irAEs

The following listings will be provided (Listing analysis set: Safety Set):

- A by-subject listing of all SAEs
- A by-subject listing of all irAEs

4.12.3 Clinical Laboratory Evaluation

The clinical laboratory tests include the following tests:

- Blood routine (eCRF: Hematology)
- Blood biochemistry (eCRF: Clinical Chemistry)
- Urinalysis (eCRF: Urinalysis and 24-hr Urinalysis)
- Coagulation function (eCRF: Coagulation)
- Myocardial Enzymogram (eCRF: Myocardial Enzymogram)
- Thyroid function (eCRF: Endocrine function tests)
- Virology testing (eCRF: Viral Serology)
- Serum Pregnancy test (eCRF: Serum Pregnancy test)

The details are shown in **Appendix 7. 2**. The baseline clinical laboratory assessments will be the last non-missing measurement prior to the administration date and time. If the baseline clinical laboratory data is missing, no imputation will be made, and therefore the change from baseline value will be missing. All clinical laboratory data will be summarized by descriptive statistics of each follow-up, including n, mean, SD, median, minimum, maximum and change from baseline for quantitative data, and count, percentage and shift at post-baseline for qualitative data.

The following summaries will be provided:

- Summary of each clinical laboratory test and its change from baseline by visit and study treatment (Analysis set: Safety Set).
- A summary of the number and percentage of subjects who are low, normal or high at baseline and the shift at post-baseline for each clinical laboratory test by visit and study treatment (Analysis set: Safety Set).
- By-subject listings of all laboratory tests (Listing analysis set: Safety Set).

All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with ‘L’ for values below the lower limit of the clinical reference range and ‘H’ for values above the upper limit of the clinical reference range and included in the listings.

4.12.4 Vital Signs, Physical Findings and Other Observations Related to Safety

4.12.4.1 Vital Signs

The vital sign variables include height, weight, systolic blood pressure, diastolic blood pressure, pulse, temperature, and respiratory rate (eCRF: Vital Sign).

The following summaries will be provided:

- A summary of each vital sign by visit and study treatment (Analysis set: Safety Set).
- A summary of change from baseline in each vital sign by visit and study treatment (Analysis set: Safety Set).
- A by-subject listing of all vital signs will be provided (Listing analysis set: Safety Set).

4.12.4.2 Physical Examinations

Physical examination variables will include the results (clinical significance) of following examination: head and neck (including thyroid), chest (including heart and lungs), abdomen (including liver, gallbladder, spleen and kidney), limbs, skin, lymph nodes, neurological system and general appearance (eCRF: Physical Examination). The Full physical examination will be performed at screening period. Symptom-directed physical examination will be carried out during study treatment.

The following summaries will be provided:

- A summary of each physical examination by body system, visit and study treatment (Analysis set: Safety Set).
- A summary of change from baseline using shift table in each physical examination by visit and study treatment (Analysis set: Safety Set).
- A by-subject listing of all physical examination will be provided (Listing analysis set: Safety Set).

4.12.4.3 12-Lead ECG

ECG parameters (Heart Rate; PR interval; RR interval; QRS duration; QT interval; QTcF) will be summarized by observed time point using appropriate descriptive statistics by treatment group (eCRF: 12-lead ECG).

The overall assessment of 12-lead ECG will be evaluated by the Investigator as ‘Normal’, ‘Abnormal - Not Clinically Significant’ or ‘Abnormal - Clinically Significant’. The baseline assessments of ECG will be the last non-missing measurement prior to the administration date/time. If the baseline measurement of ECG is missing, the change from baseline value will also be missing since no imputation will be made.

The following summaries will be provided:

- Summary of each ECG parameter, including overall assessment, by visit and study treatment (Analysis set: Safety Set).
- Summary of the change from baseline in each ECG parameter, including overall assessment, by visit and study treatment (Analysis set: Safety Set).

- Summary of the number and percentage of subjects with QTcF exceeding the predefined upper limit (>450ms, >480ms, >500ms) (Analysis set: Safety Set).
- A by-subject listing of all ECG parameters will be provided (Listing analysis set: Safety Set).

4.12.4.4 ECOG Performance Status

ECOG performance status (ECOG PS) score (0,1,2,3,4,5) should be rated prior to the first dose of study drug as **Appendix 7. 3**. If it is evaluated on Day -7 to Day -1 during screening period, a repeat evaluation will not be required.

The following summaries will be provided:

- Summary of the ECOG PS score by visit and study treatment (Analysis set: Safety Set).
- Summary of the change from baseline in the ECOG PS score by visit and study treatment (Analysis set: Safety Set).
- A by-subject listing of ECOG PS score will be provided (Listing analysis set: Safety Set).

4.13 Other Analyses

At the initial treatment period, PK and ADA samples for HLX10 or placebo will be collected at the following time points: within 7 days pre-dose in Cycle 1, within 3 days pre-dose in Cycles 2, 4, 6, 8 and every 4 cycles thereafter, within 2 hours after the end of dosing in Cycles 1 and 8 of treatment period (for PK only), at EOT visit and safety follow-up.

At the post-PD treatment period, PK and ADA samples for HLX10 or placebo will be collected at the following time points: within 3 days pre-dose in cycle 1 and thereafter every 4 cycles, at EOT visit and safety follow-up.

4.13.1 Pharmacokinetics

A by-subject listing of PK concentration will be provided based on PKS. PK concentrations below the lower limit of quantification (LLOQ) will be presented as BLQ in the listings and set to zero for descriptive statistics. Subjects ADA/NAb (positive or negative) status will be included in listings. The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of concentration data:

- Source data shall be used in all derived PK concentrations without prior rounding.
- The mean, geometric mean and median will be tabulated to one more decimal digit compared to the source data, but with a maximum of four decimal digits, standard deviation (SD) will have one more decimal digit than arithmetic mean.
- Minimum and maximum values will be tabulated to the same precision as the source data, but with a maximum of four decimal digits. Median values will have one more decimal digit than source data.
- Geometric coefficient of variation (CV_b%) and coefficient of variation (CV%) will be presented to one decimal place.

A summary of PK concentrations by timepoint and study treatment will be provided using PKS.

The following descriptive statistics will be presented for PK concentrations: n, arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV% (CV_b%, calculated as:

$\%CV_b = 100 * \sqrt{\exp(s^2) - 1}$; where s is the standard deviation of the log-transformed values), median, minimum and maximum values.

If 3 or more subjects who have received HLX10 treatment were ADA or NAb positive (if a subject has at least one positive ADA or NAb sample after receiving HLX10 treatment, he/she will be considered ADA or NAb positive subject), all PK concentrations will be stratified by ADA or NAb status for descriptive statistics.

The arithmetic means and SD of initial treatment period and post-PD treatment period will be presented using linear and semi-log coordinate. If the ADA/NAb stratification criteria is met, the mean and SD for ADA/NAb positive and negative subjects will be displayed separately.

The accumulation index (R_{Cmax} and $R_{Ctrough}$, ratio of HLX10 drug cumulation) following multiple HLX10 dosing will be calculated by the nominal sampling time, listed, and summarized by descriptive statistics including n, arithmetic mean, SD, CV%, geometric mean, geometric CV% (CV_b%), median, minimum, and maximum. R_{Cmax}=concentration after Cycle 8 dosing / concentration after Cycle 1 dosing, $R_{Ctrough}$=concentration before Cycle 8 dosing / concentration before Cycle 2 dosing. R_{Cmax} and $R_{Ctrough}$ will be presented to 2 decimal digits. If the ADA/NAb stratification criteria is met, the PK parameters (C_{max}, C_{trough}, R_{Cmax} and $R_{Ctrough}$) will be stratified by ADA or NAb status for descriptive statistics.

4.13.2 Immunogenicity

The following ADA/NAb summaries will be provided:

- A summary of the number and percentage of positive ADA/NAb by visit and study treatment (Analysis set: Safety Set).
- A by-subject listing of ADA will be provided (Listing analysis set: Safety Set).
- The number and percentage of patients with at least one positive ADA/NAb at any timepoint after receiving HLX10 administration.

4.13.3 Biomarker Analysis

In this study, the biomarkers include PD-L1 expression status, MSI and TMB. The OS and PFS assessed by IRRC and Investigator based on RECIST 1.1 will be analyzed the relationship with biomarkers.

The following summaries will be provided:

- Summary of the OS including the median OS with corresponding two-sided 95% CI if it is evaluable, and the quartile OS with corresponding two-sided 95% CI by categorical biomarker (PD-L1 status, MSI) and study treatment (Analysis set: ITT Set, PPS).
- Kaplan-Meier OS survival curve with two-sided 95% CI by categorical biomarker (PD-L1, MSI) and study treatment (Analysis set: ITT Set, PPS).
- OS hazard ratios and its 95% CI for each continuous biomarker (PD-L1 expression, TMB) will be estimated by the Cox proportional hazards model with study treatment. Efron's method will be used to handle ties (Analysis set: ITT Set, PPS).

- Summary of the PFS including the median PFS with corresponding two-sided 95% CI if it is evaluable, and the quartile PFS with corresponding two-sided 95% CI by categorical biomarker (PD-L1 status, MSI) and study treatment (Analysis set: ITT Set, PPS).
- Kaplan-Meier PFS survival curve with two-sided 95% CI by categorical biomarker (PD-L1, MSI) and study treatment (Analysis set: ITT Set, PPS).
- PFS hazard ratios and its 95% CI for each continuous biomarker (PD-L1 expression, TMB) will be estimated by the Cox proportional hazards model with study treatment. Efron's method will be used to handle ties (Analysis set: ITT Set, PPS).

4.13.4 Quality of Life Assessment

The health status and self-perceived health of each patient will be documented in the form of EQ-5D-5L scale, EORTC QLQ-C30 scale, and EORTC QLQ-LC13 scale.

Descriptive statistics are based on the allocation for the scale scores, subscale scores, and individual scores at each visit and their changes from baseline., Patient-reported outcomes (PROs) analysis of all data will be performed based on the ITT Set.

4.13.4.1 EQ-5D-5L

The 5-level EQ-5D 3rd version (EQ-5D-5L) has five descriptive dimensions of health score as:

- **Mobility:**
  - Level 1 (No problems)
  - Level 2 (Slight problems)
  - Level 3 (Moderate problems)
  - Level 4 (Severe problems)
  - Level 5 (Unable to)
- **Self-care:**
  - Level 1 (No problems)
  - Level 2 (Slight problems)
  - Level 3 (Moderate problems)
  - Level 4 (Severe problems)
  - Level 5 (Unable to)
- **Usual activities:**
  - Level 1 (No problems)
  - Level 2 (Slight problems)
  - Level 3 (Moderate problems)
  - Level 4 (Severe problems)
  - Level 5 (Unable to)

- **Pain or discomfort:**
  - Level 1 (No pain)
  - Level 2 (Slight pain)
  - Level 3 (Moderate pain)
  - Level 4 (Severe pain)
  - Level 5 (Extremely pain)
- **Anxiety or depression:**
  - Level 1 (No anxious)
  - Level 2 (Slight anxious)
  - Level 3 (Moderate anxious)
  - Level 4 (Severe anxious)
  - Level 5 (Extremely anxious)

The respondent is asked to indicate his/her health state by checking the box next to the most appropriate response level for each of the five dimensions. Responses are coded as single-digit numbers expressing the severity level selected in each dimension.

A visual analogue scale (EQ VAS) records the respondent's overall current health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The EQ VAS (0-100) provides a quantitative measure of the patient's perception of their overall health.

EQ-5D scores during treatment period and changes from baseline will be summarized by visit and treatment arms. Five descriptive dimensions of health score will be analyzed as categorical variables and the self-estimated EQ VAS will be analyzed as continuous variable. A summary statistics table and listing will be provided for all 5 dimensions' health scores and self-estimated health score by ITT Population with a corresponding listing (Listing analysis set: ITT Set).

4.13.4.2 EORTC-QLQ-C30

European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) is a cancer health-related quality-of-life questionnaire that has been widely used in clinical trials and investigations using PROs for individual patient management.

The EORTC QLQ-C30 v3 questionnaire is an established measure of health-related quality of life (HRQoL) and is commonly used as an endpoint in oncology clinical trials. The questionnaire assesses HRQoL/health status through 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, nausea and vomiting), and 1 global health and QoL (quality of life) scale. The 6 individual symptom measures include: dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties. For the 15 domains described above, the total score is standardized to a range from 0 to 100, where higher scores indicate stronger functioning, higher HRQoL or higher symptom levels.

For ease of presentation and interpretation, all scale and item scores are linearly transformed to a 0 to 100 scale, with higher scores representing increasing symptom levels. The transformed score for a subject and missing data handling can be expressed as **Appendix 7. 4 Scoring the QLQ-C30 version 3.0.**

EORTC-QLQ-C30 scores during treatment period and changes from baseline will be summarized by visit and treatment arms for ITT Population. A summary statistics table will be provided for all 5 function domains and self-estimated health score by ITT Set with a corresponding listing (Listing analysis set: ITT Set).

4.13.4.3 EORTC-QLQ-LC13

The EORTC-QLQ-LC13 is a 13-item self-administered questionnaire for lung cancer disease that will be used along with the EORTC QLQ-C30. The scale includes both multiple and single lung cancer-related symptom parameters (i.e., cough, hemoptysis, dyspnea and pain), as well as side effects of conventional chemotherapy and radiotherapy (i.e., alopecia, neurological disorders, oral pain and dysphagia). Similar to the EORTC QLQ-C30, all questions (except one) are on a 4-point scale: "not at all", "a little", "quite a bit", and "very much". Only 1 question (43rd question "Did you take any medicine for pain?") is with response options of "yes" or "no". The QLQ-LC13 are scored similarly to the EORTC-QLQ-C30. The scoring approach for QLQ-LC13 can be expressed as **Appendix 7. 5 Scoring the QLQ-LC13.**

For ease of presentation and interpretation, all scale and item scores are linearly transformed to a 0 to 100 scale, with higher scores representing increasing symptom levels.

$$\textbf{Transformed QLQ-LC13 score} = \frac{\text{Sum of item scores} - \text{Number of items}}{3 \times \text{Number of items}} \times 100$$

The observed values and changes from baseline for overall score, sub-scores and individual scores for each visit will be statistically described (Analysis set: ITT Set). The overall score is defined as the sum of all item scores except pain medication. The sub-scores are

- Lung cancer related symptoms including cough, hemoptysis and dyspnea;
- Treatment related side-effects including sore mouth or tongue, dysphagia, hair loss, tingling hands and feet;
- Pain.

The summary statistics for the overall score, sub-scores and individual scores and the changes from baseline will be tabulated by study treatment and visit.

Statistical analyses including baseline, post baseline, change from baseline are the same as the EORTC-QLQ-LC13 score. All QoL analysis will be performed based on the ITT Set. A by-subject listing of EORTC-QLQ-LC13 will be provided (Listing analysis set: ITT Set).

4.14 Safety Monitoring (Independent Data Monitoring Committee [IDMC])

The IDMC will be assembled to evaluate safety data for the study. The IDMC will also evaluate efficacy data, such as OS for the planned interim analysis. Following the data review, the IDMC will provide a recommendation as to whether the study may continue, whether amendments to the protocol should be implemented, or whether the study should be stopped. The final decision will

rest with the sponsor. The details of procedures including roles and responsibility, composition, meetings, data package of meeting, decision making and confidentiality, can be referred to a separate IDMC charter.

4.15 Determination of Sample Size

The randomization ratio for this study is 2:1. The sample size is estimated based on the assumption that the median OS for treatment with placebo + chemotherapy (Carboplatin–Etoposide) is 10 months and the hazard ratio (HR) of (HLX10 + chemotherapy) group versus the control group is 0.7, and it is further assumed that when the enrollment period is 24 months and the whole study period is 34 months, to achieve a confidence level of 85% at an overall significance level $\alpha = 0.05$ (two-sided), at least 342 OS events have to be observed. Considering a dropout rate of 20%, a total of 567 subjects (378 in treatment arm and 189 in control arm) need to be enrolled in the 2 arms.

It is planned in this study that, when the 378 subjects (about 2/3 of the number of subjects planned to be enrolled) was enrolled under supervision of the Independent Data Monitoring Committee (IDMC), the sponsor will consider performing a blinded sample size estimation, and if the blinded overall median OS is lower than the expected value, then the sponsor will communicate with principal investigator and regulatory authorities about the necessary increase in the sample size (number of OS events).

4.16 Changes in the Conduct of the Study or Planned Analysis

Not applicable.

4.17 Analyses of Data from Asian and Non-Asian

This study is a multi-regional clinical trial. Therefore, besides the global data analysis, statistical analysis will also be reported in Asian and Non-Asian population separately.

All analyses detailed in **4.1** to **4.16** will be repeated for the subjects randomized in Asian and Non-Asian.

5 Inconsistency from Protocol

The definition of PKS in protocol was:

The PKS consists of all participants who received at least one dose of study intervention with at least one post-dose concentration measurement at scheduled PK time points without any major protocol violation that may impact the PK assessment significantly. The PK analysis set will be used for PK analysis.

The concept of “study intervention” contains both HLX10 and placebo, while HLX10 concentration from placebo group are presumed to be LLOQ. To describe the population for PK analysis more precisely, the definition of PKS is changed as follows:

The PKS consists of all participants who received at least one dose of **HLX10** with at least one **measurable** post-dose concentration at scheduled PK time points without any major protocol

violation that may impact the PK assessment significantly. The PK analysis set will be used for PK analysis.

The definition of PPS in protocol was:

The PPS comprises a subset of the ITT. The PPS consists of all randomized subjects undergoing at least one post-treatment tumor assessment without any major protocol deviation that impacts the primary efficacy significantly. The PPS will be used to demonstrate robustness of results for the primary efficacy endpoint.

Whether the subject has at least one post-treatment tumor assessment that do not affect the primary efficacy OS. To describe PPS more precisely, the definition of PPS is changed as follows:

The PPS comprises a subset of the ITT. The PPS consists of all randomized subjects without any major protocol deviation that impacts the primary efficacy significantly. The PPS will be used to demonstrate robustness of results for the primary efficacy endpoint.

6 REFERENCES

Not applicable.

7 APPEXDIX

7.1 Appendix 7. 1 Schedule of Activities

Initial Treatment Period

Periods	Screening Period		Treatment Period (three-week cycles)					End-of-Treatment (EOT) visit[1]	Follow-up Period[2]	
Treatment Cycles/Visits	Screening Period		1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[3]
Time of Visit	-28 to -8	-7 to -1	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[4]				± 3	± 3	± 3	± 3	+7	± 7	± 7
Management Procedures										
Informed consent form	X									
Inclusion/exclusion criteria	X									
Dispensing of subject ID card	X									
Demographics and medical history	X									
Prior and concomitant therapies[5]	X		X	X	X	X	X	X	X	
Clinical Operations/Assessments										
Adverse events[6]	X		X	X	X	X	X	X	X	
Quality of life[7]		X	X		X		X	X	X	
Echocardiography	X									
12-lead ECG[8]		X	X	X	X	X	X	X	X	
ECOG scores[8]		X	X	X	X	X	X	X	X	
Complete physical examination	X									
Symptom-oriented physical examination			X	X	X	X	X	X	X	
Height, weight and vital signs[9]	X		X	X	X	X	X	X	X	
Subsequent antineoplastic therapy									X	X
Survival status			X	X	X	X	X	X	X	X
Study Treatment										

Periods	**Screening Period**		**Treatment Period (three-week cycles)**					**End-of-Treatment (EOT) visit**[1]	**Follow-up Period**[2]	
Treatment Cycles/Visits	Screening Period		1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[3]
Time of Visit	-28 to -8	-7 to -1	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[4]				± 3	± 3	± 3	± 3	+7	± 7	± 7
Randomization[10]			**X**							
HLX10 or placebo[10]			**X**	**X**	**X**	**X**	**X**			
Etoposide + carboplatin			**X**	**X**	**X**	**X**				
Clinical Operations/Assessments: by study site										
Pregnancy test[11]		**X**			**X**		**X**	**X**	**X**	
Routine blood test, serum biochemistry, coagulation test, myocardial function (CK, CKMB, TnI/TnT) and BNP (or NT pro BNP), urinalysis[12]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
T3 or FT3, T4 or FT4, TSH[13]		**X**			**X**		**X**	**X**	**X**	
HBV antibody, HBV DNA[14]	**X**									
● In case of HBV DNA (-) and: 1) HBsAg (+), or 2) HBcAb (+) and HBsAg (-) at baseline, HBV antibody and HBV DNA should be examined during the treatment period.					**X**		**X**	**X**	**X**	
HCV antibody, HCV RNA[14]	**X**									
● In case of HCV antibody (+) and HCV RNA (-) at baseline, HCV antibody and HCV RNA should be					**X**		**X**	**X**	**X**	

Periods	**Screening Period**		**Treatment Period (three-week cycles)**					**End-of-Treatment (EOT) visit[1]**	**Follow-up Period[2]**	
Treatment Cycles/Visits	Screening Period		1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[3]
Time of Visit	-28 to -8	-7 to -1	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[4]				± 3	± 3	± 3	± 3	+7	± 7	± 7
examined during the treatment period.										
HIV	**X**									
Tuberculosis[15]	**X**									
Clinical Operations/Assessments: by central laboratory										
HLX10-PK, ADA[16]			**X**	**X**		**X**	**X**	**X**	**X**	
Efficacy Assessment										
Radiological Examination[17]	**X**				**X**		**X**	**X**		
Biomarker Sample Collection										
Tumor tissue[18]	**X**									
Blood	**X**									

ADA=anti-drug antibody, DNA=deoxyribonucleic acid, ECOG=Eastern Cooperative Oncology Group, HBcAb=hepatitis B core antibody, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, PK=pharmacokinetics, RNA=ribonucleic acid.

1. If a subject discontinues study treatment for any reason, an end-of-treatment (EOT) visit should be performed whenever possible and should be completed within 7 days after informed or discontinuation confirmed (and should be completed before the subject starts a new anti-tumor therapy);
2. All subjects are required to visit the study site for safety follow-up 30 days (± 7 days) after the last study drug administration; if the end-of-treatment visit is delayed for any reasons and occurs after the time window of 30 days (± 7 days), no further safety follow-up visit is required. All subjects are required to receive a follow-up telephone call for safety follow-up 90 days (± 7 days) after the last study drug administration. Only the information of AEs and AE-related concomitant drugs is collected.
3. Subjects should be followed for survival by telephone every 12 weeks ± 7 days after starting a new antineoplastic therapy or treatment termination criteria are met; the frequency of survival follow-up may be increased as appropriate.

Periods	**Screening Period**		**Treatment Period (three-week cycles)**					**End-of-Treatment (EOT) visit[1]**	**Follow-up Period[2]**	
Treatment Cycles/Visits	Screening Period		1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[3]
Time of Visit	-28 to -8	-7 to -1	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[4]				± 3	± 3	± 3	± 3	+7	± 7	± 7

4. The maximum screening period is 28 days; the time windows are ± 3 days for treatment, ± 7 days for tumor assessment, + 7 days for EOT visit, and ± 7 days for follow-up. ECOG performance status, serum pregnancy test, blood routine, biochemistry, coagulation, myocardial function, urinalysis and thyroid function (T3 or FT3, T4 or FT4, TSH) should be completed within 7 days before randomization, and the subjects should meet the corresponding inclusion/exclusion criteria for enrollment.
5. All prior and concomitant medications are recorded from 30 days prior to signing the informed consent form (ICF) through the safety follow-up visit; concomitant medications associated with AEs are recorded up to 90 days after the last study treatment.
6. All AEs and treatment emergent AEs are recorded from the time of signing the ICF until 90 days after the last study treatment. If a subject starts a new antineoplastic therapy during the AE collection period, only information on AEs related to study treatment are collected after the new antineoplastic therapy.
7. Quality of life scales including the EQ-5D-5L, the European Organization for Research and Treatment of Cancer Quality of Life Scale (EORTC QLQ-C30), and the European Organization for Research and Treatment of Cancer lung cancer questionnaire module (EORTC QLQ-LC13). Such scales are evaluated prior to the first dose and every other subsequent dosing cycle (i.e., pre-dose in Cycles 1, 3, 5, 7, etc.) until EOT. A quality of life assessment is required at the EOT visit if no assessment has been performed within the past 3 weeks. Quality of life assessment could be performed either on Day -7 to Day -1 of the screening period or prior to dosing in Cycle 1.
8. Re-assessments prior to dosing in Cycle 1 are not required for subjects who had 12-lead ECG and ECOG scores assessment on Day -7 to Day -1 of the screening period.
9. **The height measurement is performed only at screening**; vital signs include body temperature, pulse, respiratory rate, and blood pressure. Body weight will be measured prior to drug administration at each treatment cycle. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose of investigational product, the dose of investigational product must be recalculated. All doses should be rounded to the nearest milligram.
10. Study drug is administered on Day 1 of each 3-week cycle after all clinical and laboratory operations/assessments are completed. No more than 3 days must have elapsed between the date of randomization and the date of the first study dose.
11. Women of childbearing potential must have a serum pregnancy test. This is also performed within 3 days prior to dosing every other cycle during the treatment period.
12. Routine blood test items include red blood cell count, hemoglobin, platelet, white blood cell count, white blood cell differential counts and percentages (including: basophils, eosinophils, lymphocytes, monocytes, neutrophils); serum biochemistry items include blood urea/urea nitrogen, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, blood glucose, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase, total cholesterol, total protein, albumin; coagulation test consist of prothrombin time (PT), activated partial thromboplastin time (APTT) and

Periods	**Screening Period**		**Treatment Period (three-week cycles)**					**End-of-Treatment (EOT) visit[1]**	**Follow-up Period[2]**	
Treatment Cycles/Visits	Screening Period		1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[3]
Time of Visit	-28 to -8	-7 to -1	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[4]				± 3	± 3	± 3	± 3	+7	± 7	± 7

international normalized ratio (INR); myocardial function detection includes troponin-I (TnI)/troponin-T (TnT), creatine kinase isoenzyme (CK-MB)/ and creatine kinase (CK), Brain Natriuretic Peptide (BNP)/N-terminal pro-Brain Natriuretic Peptide (NT-pro BNP); urinalysis items include specific gravity, urine leukocytes, pH, urine glucose, urine protein, ketone body and urine occult blood, microscopic examination of white blood cells and red blood cells should be collected if urine leukocytes and urine occult blood are out of normal range. These tests should be performed **within 3 days before dosing in each cycle**; for aforementioned laboratory tests scheduled on the same day as study treatment, the study treatment can be arranged only after the test results are obtained. For laboratory tests from the screening period completed on Day -7 ~ Day -1, it is not necessary to repeat the test again before the first administration (C1D1). For combined chemotherapy, routine blood tests should be performed on Day 8 (± 3 days) of each treatment cycle to closely monitor bone marrow suppression.

13. Thyroid function tests include triiodothyronine (T3 or FT3), thyroxine (T4 or FT4) and thyroid stimulating hormone (TSH) assays. This is also performed within 3 days prior to dosing every other cycle during the treatment period.
14. All subjects are tested for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody at screening. Patients with HBsAg (+) and/or HBcAb (+) should be further tested for hepatitis B virus (HBV) DNA titer; and HCV antibody positive subjects should be further tested for HCV RNA. In case of HBV DNA (-) and: 1) HBsAg (+), or 2) HBcAb (+) and HBsAg (-) at baseline, HBV antibody and HBV DNA should be tested every 2 cycles during the treatment period. In case of HCV antibody (+) and HCV RNA (-) at baseline, HCV antibody and HCV RNA should be tested every 2 cycles during the treatment period.
15. Bulgarian subjects should be tested for active and latent tuberculosis using a method as per standard local practice (as requested by the Bulgarian Drug Agency for Bulgarian subjects).
16. PK and ADA sampling: (**Note: ADA samples will only be collected pre-dose** and procedures are described in the laboratory manual)
    - PK and ADA samples for HLX10 or placebo will be collected at the following time points: within 7 days **pre-dose** in Cycle 1, within 3 days **pre-dose** in Cycles 2, 4, 6, 8 and every 4 cycles thereafter, within 2 hours **after the end** of dosing in Cycles 1 and 8 of treatment period **(for PK only)**, at EOT visit and safety follow-up.
17. Computerized tomography (CT) or magnetic resonance imaging (MRI) should be performed at screening, every 6 weeks (± 7 days) during the first 48 weeks after the start of study treatment, and every 9 weeks (± 7 days) after week 48 on sites including brain, chest, abdomen, pelvic cavity and any other sites suspected to have tumor lesions, in which **brain MRI or CT (preferably MRI) and bone scans** are required for all subjects at screening, and are performed in the treatment period as determined by the investigator according to clinical needs (if baseline brain CT/MRI shows that brain metastasis is not present, the subject should have follow up brain imaging only

Periods	**Screening Period**		**Treatment Period (three-week cycles)**					**End-of-Treatment (EOT) visit[1]**	**Follow-up Period[2]**	
Treatment Cycles/Visits	Screening Period		1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[3]
Time of Visit	-28 to -8	-7 to -1	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[4]				± 3	± 3	± 3	± 3	+7	± 7	± 7

if clinically indicated at the discretion of the investigator. If baseline brain CT/MRI has confirmed central nervous system (CNS) metastasis, continuous brain imaging test should be carried out as part of the regular RECIST evaluation assessments); examination methods at the same site should be consistent as much as possible throughout the study; if there are no contraindications, contrast agent should be used. The investigator and IRRC respectively assess the tumor images according to RECIST 1.1 (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation. If tumor assessment has been performed within 28 days prior to the first dose by the same methods and devices in the same hospital, it may serve as the baseline tumor assessment. At the EOT visit, if tumor imaging has been performed within the last 4 weeks, a re-test is not required. For subjects who discontinued for reasons other than disease progression, radiological assessments are to be continued as scheduled, until disease progression, initiation of new antineoplastic therapy, withdrawal of ICF, death, or end of study, whichever occurs first.

18. Patients must provide tumor tissues that meet the requirements for the determination of PD-L1 expression levels. It is recommended to provide formalin-fixed tumor tissue samples, paraffin-embedded tumor specimens (preferred), formalin-fixed paraffin embedded (FFPE), tumor specimens or newly prepared unstained serial tissue sections (preferably adhesive slides) within 6 months prior to the first dose of study medication. A relevant pathology report must also be provided for the above specimens. Freshly collected specimens, radical resections, core needle biopsy, excisions, incisions, punch or clamp biopsies are acceptable (newly obtained tissues are preferred). Fine-needle aspirations (i.e., samples that lack a complete tissue structure and provide only cell suspension and/or cell smear), brush biopsies, and cell pellet samples from pleural or peritoneal effusions are unacceptable. For detailed requirements for tissue samples, see the laboratory manual.

Post-PD Treatment Period (Optional)

Periods	**Post-PD Treatment Period (three-week cycles)[1]**					**End-of-Treatment (EOT) visit[2]**	**Follow-up Period[3]**	
Treatment Cycles/Visits	1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[4]
Time of Visit	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[5]		± 3	± 3	± 3	± 3	+7	± 7	± 7
Management Procedures								
Supplementary informed consent form	**X**							
Eligibility criteria	**X**							
Concomitant therapies[6]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Clinical Operations/Assessments								
Adverse events[7]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
12-lead ECG	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Symptom-oriented physical examination	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Weight and vital signs[8]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
ECOG scores	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Subsequent antineoplastic therapy	**X**[9]						**X**	**X**

Periods	**Post-PD Treatment Period (three-week cycles)[1]**					**End-of-Treatment (EOT) visit[2]**	**Follow-up Period[3]**	
Treatment Cycles/Visits	1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[4]
Time of Visit	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[5]		± 3	± 3	± 3	± 3	+7	± 7	± 7
Survival status	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Study Treatment								
HLX10 or placebo[10]	**X**	**X**	**X**	**X**	**X**			
Clinical Operations/Assessments: by study site								
Pregnancy test[11]	**X**		**X**		**X**	**X**	**X**	
Routine blood test, serum biochemistry, coagulation test, myocardial function, urinalysis[12]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
T3 or FT3, T4 or FT4, TSH[13]	**X**		**X**		**X**	**X**	**X**	
HBV antibody, HBV DNA[14]								
● In case of HBV DNA (-) and: 1) HBsAg (+), or 2) HBcAb (+) and HBsAg (-) at baseline, HBV antibody and HBV DNA should be examined during the treatment period.	**X**		**X**		**X**	**X**	**X**	
HCV antibody, HCV RNA[14]								

Periods	**Post-PD Treatment Period (three-week cycles)[1]**					**End-of-Treatment (EOT) visit[2]**	**Follow-up Period[3]**	
Treatment Cycles/Visits	1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[4]
Time of Visit	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[5]		± 3	± 3	± 3	± 3	+7	± 7	± 7
● In case of HCV antibody (+) and HCV RNA (-) at baseline, HCV antibody and HCV RNA should be examined during the treatment period.	**X**		**X**		**X**	**X**	**X**	
HLX10-PK, ADA[15]	**X**				**X**	**X**	**X**	
Efficacy Assessment								
Radiological Examination[16]	**X**		**X**		**X**	**X**		

Periods	**Post-PD Treatment Period (three-week cycles)[1]**					**End-of-Treatment (EOT) visit[2]**	**Follow-up Period[3]**	
Treatment Cycles/Visits	1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[4]
Time of Visit	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[5]		± 3	± 3	± 3	± 3	+7	± 7	± 7
● In case of HCV antibody (+) and HCV RNA (-) at baseline, HCV antibody and HCV RNA should be examined during the treatment period.	**X**		**X**		**X**	**X**	**X**	
HLX10-PK, ADA[15]	**X**				**X**	**X**	**X**	
Efficacy Assessment								
Radiological Examination[16]	**X**		**X**		**X**	**X**		

Periods	**Post-PD Treatment Period (three-week cycles)[1]**					**End-of-Treatment (EOT) visit[2]**	**Follow-up Period[3]**	
Treatment Cycles/Visits	1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[4]
Time of Visit	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[5]		± 3	± 3	± 3	± 3	+7	± 7	± 7

1. After finishing the initial treatment period, patients in both arms who had 1st disease progression per RECIST 1.1 who, in the investigator's opinion, would continue to receive benefit from their assigned treatment in addition to 2nd line chemotherapy may be eligible to continue to receive their assigned treatment in the post-PD treatment period (Optional) until the 2nd disease progression, intolerable toxicity, death, withdrawal of consent, or lost to follow-up. The following visits and assessments are recommended for post-PD treatment period.
2. If a subject discontinues study treatment for any reason, an end-of-treatment (EOT) visit should be performed whenever possible and should be completed within 7 days after informed or discontinuation confirmed (and should be completed before the subject starts a new anti-tumor therapy).
3. All subjects are required to visit the study site for safety follow-up 30 days (± 7 days) after the last study drug administration; if the EOT visit is delayed for any reason and occurs after the time window of 30 days (± 7 days), no further safety follow-up visit is required. All subjects are required to receive a follow-up telephone call for safety follow-up 90 days (± 7 days) after the last study drug administration. Only the information of AEs and AE-related concomitant drugs is collected.
4. Subjects should be followed for survival by telephone every 12 weeks ± 7 days after starting a new antineoplastic therapy or treatment termination criteria are met; the frequency of survival follow-up may be increased as appropriate.
5. The time windows are ± 3 days for treatment, ± 7 days for tumor assessment, + 7 days for EOT visit, and ± 7 days for follow-up. The subjects should meet the corresponding eligibility criteria for enrollment.
6. All concomitant medications are recorded up to the safety follow-up visit, and concomitant medications associated with AEs are recorded up to 90 days after the last study treatment.
7. All AEs and treatment emergent AEs are recorded up to 90 days after the last study treatment. If a subject starts a new antineoplastic therapy during the AE collection period, only information on AEs related to study treatment are collected after the new antineoplastic therapy.
8. Vital signs include body temperature, pulse, respiratory rate, and blood pressure. Body weight will be measured prior to drug administration at each treatment cycle. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose of investigational product, the dose of investigational product must be recalculated. All doses should be rounded to the nearest milligram.

Periods	**Post-PD Treatment Period (three-week cycles)[1]**					**End-of-Treatment (EOT) visit[2]**	**Follow-up Period[3]**	
Treatment Cycles/Visits	1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[4]
Time of Visit	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[5]		± 3	± 3	± 3	± 3	+7	± 7	± 7

9. Subsequent antineoplastic therapy in post-PD treatment period must be 2nd line chemotherapy. 2nd line chemotherapy (anti-PD1 and anti-PD-L1 therapy are not included) was determined by investigators after communicating with the subjects, NCCN guidelines or ESMO guidelines are the preferred reference.
10. Subjects must not initiate treatment with HLX10 or placebo in post-PD treatment any earlier than 21 days and no more than 12 weeks after their last dose of initial treatment (including chemotherapy) regardless of the time of progression. HLX10 or placebo is administered on Day 1 of each 3-week cycle after all clinical and laboratory operations/assessments are completed.
11. Women of childbearing potential must have a serum pregnancy test. This is also performed within 3 days prior to dosing every other cycle during the treatment period. If the test is done within 3 days before the first dose of investigational drug, it is not necessary to perform the test again.
12. Routine blood test items include red blood cell count, hemoglobin, platelet, white blood cell count, white blood cell differential counts and percentages (including: basophils, eosinophils, lymphocytes, monocytes, neutrophils); serum biochemistry items include blood urea/urea nitrogen, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, blood glucose, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase, total cholesterol, total protein, albumin; coagulation test consist of prothrombin time (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR); myocardial function detection (TnI/TnT, CK-MB/CK) and BNP/NT-pro BNP; urinalysis items include specific gravity, urine leukocytes, pH, urine glucose, urine protein, ketone body and urine occult blood, microscopic examination of white blood cells and red blood cells should be collected if urine leukocytes and urine occult blood are out of normal range. These are performed within 3 days before dose in each cycle; for aforementioned laboratory tests scheduled on the same day as study treatment, the study treatment can be arranged only after the test results are obtained. If concomitant chemotherapy requires additional laboratory tests, follow local clinical guidelines. If the test is done within 3 days before the first dose of investigational drug, it is not necessary to perform the test again.
13. Thyroid function tests include triiodothyronine (T3 or FT3), thyroxine (T4 or FT4) and thyroid stimulating hormone (TSH) assays. This is also performed within 3 days prior to dosing every other cycle during the treatment period. If the test is done within 3 days before the first dose of investigational drug, it is not necessary to perform the test again.

Periods	**Post-PD Treatment Period (three-week cycles)[1]**					**End-of-Treatment (EOT) visit[2]**	**Follow-up Period[3]**	
Treatment Cycles/Visits	1	2	3	4	n	Discontinuation	Safety follow-up	Survival follow-up[4]
Time of Visit	Every 21 days					After informed or discontinuation confirmed	30 days, 90 days after the last study drug administration (by telephone calls)	Every 12 weeks
Time Window[5]		± 3	± 3	± 3	± 3	+7	± 7	± 7

14. Patients with HBsAg (+) and/or HBcAb (+) should be further tested for hepatitis B virus (HBV) DNA titer; and HCV antibody positive subjects should be further tested for HCV RNA. In case of HBV DNA (-) and: 1) HBsAg (+), or 2) HBcAb (+) and HBsAg (-) at baseline, HBV antibody and HBV DNA should be tested every 2 cycles during the treatment period. In case of HCV antibody (+) and HCV RNA (-) at baseline, HCV antibody and HCV RNA should be tested every 2 cycles during the treatment period. If the test is done within 3 days before the first dose of investigational drug, it is not necessary to perform the test again.
15. PK and ADA sampling: PK and ADA samples for HLX10 or placebo will be collected at the following time points: within 3 days pre-dose in cycle 1 and thereafter every 4 cycles, at EOT visit and safety follow-up.
16. The tumor image used to determine disease progression can be used as the new baseline image for the post-PD treatment period if 1) the this is done within 28 days prior to receiving the first dose of HLX10 or placebo therapy and 2) there is no study treatment between the image and first dose of HLX10 or placebo therapy, otherwise a new baseline image must be performed prior to HLX10 or placebo treatment. Computerized tomography (CT) or magnetic resonance imaging (MRI) performed every 6 weeks (± 7 days) during the first 48 weeks after the start of study treatment, and every 9 weeks (± 7 days) after week 48 on sites including brain, chest, abdomen, pelvic cavity and any other sites suspected to have tumor lesions, in which brain MRI or CT (preferably MRI) and bone scans are performed in the treatment period as determined by the investigator according to clinical needs (if baseline brain CT/MRI shows that brain metastasis is not present, the subject should have follow up brain imaging only if clinically indicated at the discretion of the investigator. If baseline brain CT/MRI has confirmed central nervous system (CNS) metastasis, continuous brain imaging test should be carried out as part of the regular RECIST evaluation assessments); examination methods at the same site should be consistent as much as possible throughout the study; if there are no contraindications, contrast agent should be used. The investigator will assess the tumor images according to RECIST 1.1 (the tumor assessment can be performed by the investigator according to clinical needs), and the investigator should make subsequent treatment judgment according to the results of their own efficacy evaluation. At the EOT visit, if tumor imaging has been performed within the last 4 weeks, a re-test is not required. For subjects who discontinued for reasons other than disease progression, radiological assessments are to be continued as scheduled, until disease progression, initiation of new antineoplastic therapy, withdrawal of ICF, death, or end of study, whichever occurs first.

7.2 Appendix 7. 2 List of Laboratory Tests

Routine blood test	**Biochemistry**	**Urinalysis[a]**	**Others**
Red blood cell count (RBC) Hemoglobin (HGB) Platelet (PLT) White blood cell count (WBC) White blood cell differential count and percentage • Basophils (BAS&BAS%) • Eosinophils (EOS&EOS%) • Lymphocytes (LYM&LYM%) • Monocytes (MON&MONO%) • Neutrophils (NEU&NEUT%)	Urea (UREA)/Blood urea nitrogen (BUN) Creatinine (CR) Fasting blood glucose (GLU) Total bilirubin (TB) Direct bilirubin (TB) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Total cholesterol (CHOL) Total protein (TP) Albumin (ALB) Sodium (Na) Potassium (K) Magnesium (Mg) Chloride (Cl) Calcium (Ca) Phosphorus (P)	Specific gravity (SG) Urine leukocytes Urine pH value Urine protein (U-PRO) Urinary glucose (U-GLU) Ketones (KET) Urine occult blood (BLO) Microscopic examination of white blood cells (U-WBC) Microscopic examination of red blood cells (U-RBC)	**Coagulation function** Prothrombin Time（PT） Activated Partial Thromboplastin Time (APTT) International Normalized Ratio (INR) **Myocardial function** Troponin-I (TnI)/troponin-T (TnT), creatine kinase isoenzyme (CK-MB)/creatine kinase (CK), myoglobin Brain Natriuretic Peptide (BNP)/N-terminal pro-Brain Natriuretic Peptide (NT-pro BNP) **Thyroid function tests[b]** Triiodothyronine (T3 or FT3) Thyroxine (T4 or FT4) Thyroid-stimulating hormone (TSH) **Virology[c]** Hepatitis B Surface Antigen (HBsAg) Anti-HBs (HBsAb) Anti-HBc (HBcAb) Anti-Hepatitis C (HCV) Antibody

Routine blood test	**Biochemistry**	**Urinalysis[a]**	**Others**
			HBV DNA (optional) HCV RNA (optional) Anti-HIV
			Pregnancy test[d]
			Tuberculosis test[e]

a. If a subject has two consecutive 2++ urine protein or one ≥ 3+++, urine protein should be tested at 24 hours;

   Microscopic examination of white blood cells (U-WBC) should be collected if urine leukocytes is out of normal range. Microscopic examination of red blood cells (U-RBC) should be collected if urine occult blood is out of normal range.

b. Thyroid function tests will be performed during screening and within 3 days prior to drug administration every 2 treatment cycles during the treatment period;

c. All subjects are tested for HBsAg or HCV antibody at screening; Patients with HBsAg (+) and/or HBcAb (+) should be further tested for HBV DNA titer; and HCV antibody positive subjects should be further tested for HCV RNA. In case of HBV DNA (-) and: 1) HBsAg (+), or 2) HBcAb (+) and HBsAg (-) at baseline, HBV antibody and HBV DNA should be tested every 2 cycles during the treatment period. In case of HCV antibody (+) and HCV RNA (-) at baseline, HCV antibody and HCV RNA should be tested every 2 cycles during the treatment period.

d. Women of childbearing potential should have a blood pregnancy test within 7 days prior to randomization and must have a negative result for enrollment; this is also tested within 3 days pre-dose every 2 cycles.

**Routine blood test, blood chemistry, coagulation function, myocardial function and urinalysis must be performed at screening and within 3 days prior to drug administration every treatment cycle. When the aforementioned laboratory tests and study drug administration are scheduled on the same day, the study drug administration must be scheduled only after the test results are obtained. Data from screening period should be completed on Day -7 ~ Day -1, and it is not necessary to perform the test again before the first administration (C1D1). Routine blood tests will be performed on Day 8 (±3 days) of each treatment cycle during treatment with carboplatin, and close attention should be paid to bone marrow suppression.

e. Bulgarian subjects must undergo tuberculosis testing for active and latent tuberculosis using a testing method as per local standard practice (as requested by the Bulgarian Drug Agency for Bulgarian subjects).

7.3 Appendix 7. 3 ECOG Performance Status Score

Score	ECOG Status
0	Mobility is completely normal, and there is no difference before and after the onset of the disease.
1	Free to walk and engage in light physical activities, including general housework or office work, but not heavy physical activities.
2	Able to walk and independently take care of oneself but cannot do any work. Able to get up and move around for at least half of the time during the day.
3	Able to only finish some of self-care activities and spend more than half of the time during the day in bed or in a wheelchair.
4	Complete disability. Cannot take care of oneself at all. Totally confined to bed or in a wheelchair.
5	Death

ECOG = Eastern Cooperative Oncology Group

7.4 Appendix 7. 4 Scoring the QLQ-C30 version 3.0

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.
Thus a **high score for a functional scale** represents a *high / healthy level of functioning*,
a **high score for the global health status / QoL** represents a *high QoL*,
but a **high score for a symptom scale / item** represents a *high level of symptomatology / problems*.

The principle for scoring these scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the *raw score*.

2. Use a linear transformation to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

Technical Summary

In practical terms, if items I_1, I_2, ... I_n are included in a scale, the procedure is as follows:

Raw score
Calculate the raw score
$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$

Linear transformation
Apply the linear transformation to 0-100 to obtain the score S,

Functional scales: $$S = \left\{1 - \frac{(RS - 1)}{range}\right\} \times 100$$

Symptom scales / items: $S = \{(RS - 1)/range\} \times 100$

Global health status / QoL: $S = \{(RS - 1)/range\} \times 100$

Range is the difference between the maximum possible value of *RS* and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of *RS* equals the range of the item values. Most items are scored 1 to 4, giving *range* = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have *range* = 1.

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$$

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$$

Then for **Functional scales**:

$$Score = \left\{1 - \frac{(RS - 1)}{range}\right\} \times 100$$

and for **Symptom scales / items** and **Global health status / QoL:**

$$Score = \{(RS - 1)/range\} \times 100$$

Summary – Missing items

Have at least half of the items from the scale been answered?
If *Yes*, use all the items that were completed, and apply the standard equations given on the previous pages for calculating the scale scores; ignore any items with missing values when making the calculations.
If *No*, set scale score to missing.
For single-item measures, set score to missing.

Examples:

Emotional functioning

$$RawScore = (Q_{21} + Q_{22} + Q_{23} + Q_{24})/4$$
$$\text{EF } Score = \{1 - (RawScore - 1)\beta\} \times 100$$

Fatigue

$$RawScore = (Q_{10} + Q_{12} + Q_{18})/3$$
$$\text{FA } Score = \{(RawScore - 1)\beta\} \times 100$$

7.5 Appendix 7. 5 Scoring the QLQ-LC13

Scoring of the lung cancer module

The lung cancer module incorporates one multi-item scale to assess dyspnoea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and haemoptysis.

The scoring approach for the QLQ-LC13 is identical in principle to that for the symptom scales / single items of the QLQ-C30.

Scale name	Scale	Number of items	Item range*	QLQ-LC13 Item numbers	†
Symptom scales / items					
Dyspnoea†	LCDY	3†	3	3,4,5	X
Coughing	LCCO	1	3	1	
Haemoptysis	LCHA	1	3	2	
Sore mouth	LCSM	1	3	6	
Dysphagia	LCDS	1	3	7	
Peripheral neuropathy	LCPN	1	3	8	
Alopecia	LCHR	1	3	9	
Pain in chest	LCPC	1	3	10	
Pain in arm or shoulder	LCPA	1	3	11	
Pain in other parts	LCPO	1	3	12	

* "Item range" is the difference between the possible maximum and the minimum response to individual items.

† The dyspnoea scale should only be used if all three items have been answered. Some respondents ignore question 5 because they never climb stairs; in this case, the score for the dyspnoea scale would be biased if it were based upon the other two items. Hence if item 5 is missing then items 3 and 4 should be used as single-item measures.

7.6 Appendix 7. 6 TEAE Partial Date Conventions

- **Algorithm for Treatment Emergence of Adverse Events:**

Start Date	Stop Date	Action
Known	**Known**	• If start date < study med start date, then not TEAE. • If start date ≥ study med start date, then TEAE.
	Partial	• If start date < study med start date, then not TEAE. • If start date ≥ study med start date, then TEAE.
	Missing	• If start date < study med start date, then not TEAE. • If start date ≥ study med start date, then TEAE.
Partial, but known components show that it cannot be on or after study med start date	**Known**	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	**Known**	• If stop date < study med start date, then not TEAE. • If stop date ≥ study med start date, then TEAE.
	Partial	Impute stop date as latest possible date (*i.e.* last day of month if day unknown or 31st December if day and month are unknown), then: • If stop date < study med start date, then not TEAE. • If stop date ≥ study med start date, then TEAE.
	Missing	Assumed TEAE
Missing	**Known**	• If stop date < study med start date, then not TEAE. • If stop date ≥ study med start date, then TEAE.
	Partial	Impute stop date as latest possible date (*i.e.* last day of month if day unknown or 31st December if day and month are unknown), then: • If stop date < study med start date, then not TEAE. • If stop date ≥ study med start date, then TEAE.
	Missing	Assumed TEAE.